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PROGRESSIVE DYSTROPHY OF THE EXTERNAL OCULAR MUSCLES

(Ocular Myopathy)

BY

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INTRODUCTION

INVOLVEMENT of the external ocular muscles in progressive muscular dystrophy is considered to be rare because these muscles are not often affected during the course of any of the classical types of this disease. There are only a few instances in the literature in which this has occurred. In 1889 Winkler and Van der Weyde described a patient in whom facial weakness appeared in early youth. At the age of 19 years, the shoulder girdles, trunk and leg muscles became affected. Four years later, bilateral ptosis and limitation of the ocular movements were noted and these symptoms progressed for a year until both the ptosis and external ophthalmoplegia were severe, though not quite complete.

Seeligmüller (1889) described the case of a young woman aged 23, who had noticed progressive weakness of all four limbs for four years. The entire facial musculature was very weak, the sternomastoids were thin and ribbon-like and there was symmetrical wasting of the shoulder girdles, upper arms and quadriceps muscles. The ocular muscles became affected a year after the onset of weakness in the limbs, resulting in ptosis of the right upper lid and an incomplete bilateral external ophthalmoplegia.

Both these cases might justifiably be classified as examples of the Landouzy-Déjerine type of myopathy, in which ocular palsies have also been noted by a few authors (Landouzy and Déjerine, 1885; Bouveret, 1895; Sano, 1897; Pierre Marie, 1901).

In dystrophia myotonica, ptosis and impaired ocular movements are occasionally present in advanced cases and rare atypical types of myopathy, such as that described by Nikitin (1929) may also show ocular involvement. On the whole, affection of the eyes in the well-known types of progressive muscular dystrophy is extremely uncommon.

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A number of cases of myopathy have, however, been described, in which ocular involvement was the primary and predominant feature. In some of these, only the levators of the upper lids were affected, but in others a complete external ophthalmoplegia developed over many years. The question arises whether these cases constitute a clinical group justifying the title "ocular myopathy" or whether they are merely rare atypical forms of muscular dystrophy. This question is linked with the problem of the pathology of those cases described as chronic progressive external ophthalmoplegia and considered by most authors to result from degeneration of the oculomotor nuclei, although no clear pathological anatomy has been established for the condition. It is possible that cases of "progressive nuclear ophthalmoplegia" are in fact examples of ocular myopathy.

It is the purpose of this paper to discuss these questions, after describing 5 cases of ocular myopathy and reviewing the relevant literature.

Case 1.—S. S., a male aged 56, was admitted to King's College Hospital on February 27, 1950. He stated that in 1940 both his upper eyelids began to droop. This symptom slowly progressed without any fluctuation until 1947, after which it remained stationary. In March 1945, his wife pointed out to him that he was unable to move his eyes properly and subsequently he realized that whenever he wanted to look at anything, it was necessary for him to turn his whole head. He has never suffered from double vision. Since 1947 his neck has become thinner but he has noticed no weakness of the muscles of his trunk or limbs. He has been able to continue his trade as an upholsterer and he sought medical advice only because the drooping of his eyelids was sufficiently severe to interfere with his vision. There was nothing relevant in the patient's previous medical history. No similar condition is known to have occurred in his family.

On examination, it was noted that there was considerable bilateral ptosis and, when looking straight ahead, both pupils were almost completely covered. The palpebral fissures were 3 mm. in width but widened to 5 mm. on attempting to look up (fig. 1). All eye movements were greatly restricted, both eyeballs being equally affected. The eyes could be turned upwards through 6 degrees while depression below the horizontal was impossible. Laterally, each eye could be moved through 9 degrees but in a medial direction only barely perceptible movements could be made. Slight rotary movements, both inwards and outwards, were also possible. There was no strabismus. The pupils were equal in size and circular. They reacted briskly to light and on accommodation, though no actual convergence was possible. The temporalis and masseter muscles showed moderate wasting and weakness but opening and side-to-side movements of the jaw were normal.

Marked wrinkling of the forehead was constant and the eyebrows were raised above the level of the supraorbital ridges. In spite of this, the frontalis muscle was somewhat weak though the corrugator appeared to be normal. The orbicularis oculi muscles were very weak but eye closure was just possible. The remaining facial muscles were only slightly affected and the patient was able to smile and whistle. His neck was thin and there was obvious wasting of the upper trapezii and other posterior cervical muscles. The sternomastoids were reduced to thin strips and extension and rotation of the head were very weak. All movements of the neck were weaker than normal, especially lateral flexion. Elevation of the arms

FIG. 1 (*Case* 1).—Patient is attempting to look up.

above shoulder level was possible but difficult. The deltoids, spinati, serrati anterior and pectorales were weak and both upper limbs showed slight generalized wasting and loss of power. The remaining trunk muscles and the muscles of the lower limbs were normal.

The tendon reflexes in the upper limbs were all present but were slightly less brisk on the right than on the left. In every other respect the nervous system was normal. There was no pseudohypertrophy and no myotonia. The testicles were normal and there was no evidence of cataract. The blood picture was normal and the Wassermann reaction negative. X-rays of the skull, orbits and chest were normal. No significant alteration in the electrical excitability of the facial muscles was found. The electrocardiogram was normal.

On March 6, 1950, the patient underwent an operation for correction of the ptosis by Mr. Savin and small pieces of the right orbicularis oculi and right medial rectus muscles were removed for histological examination. They were fixed in formol saline and embedded in paraffin. Sections were stained with hæmatoxylin and eosin, Heidenhain's iron hæmatoxylin, Mallory's phosphotungstic hæmatoxylin and by Holmes' method for axis cylinders.

Right orbicularis oculi muscle.—The sections of this muscle showed advanced degenerative changes with a general increase in fibrous tissue. The bundles of muscle fibres were shrunken and contained, alongside one another, fibres which were markedly atrophied and others approximately normal in size. They varied in diameter from 7μ to 47μ, the range of normal fibres being 20μ to 40μ. In transverse section, the most atrophied fibres were round, oval or somewhat irregular in shape and stained deeply with eosin. They contained central, dark-staining nuclei. Some residual fragments of muscle fibres contained numerous proliferated sarcolemmal nuclei, many of which were pyknotic. Similar nuclear proliferation was also seen in other fibres in which the degeneration was granular rather than hyaline. For the most part, the larger fibres were normal in structure but showed

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occasional vacuolar degeneration with some proliferation of the sarcolemmal nuclei. When stained with Heidenhain's iron hæmatoxylin, many of the fibres showed poor striation while the smaller atrophied fibres, for the most part, remained unstained. Many bundles of nerve fibres were present in the section. They were well stained and showed no evidence of degeneration. This finding was confirmed in the sections stained by Holmes' axis cylinder method.

These changes in the orbicularis oculi muscle, especially the atrophy of individual muscle fibres, the vacuolar and hyaline degeneration of the sarcoplasm, the proliferation of the sarcolemmal nuclei and the preservation of normal structure in the nerve bundles, leave no doubt as to the myopathic nature of the pathological process (fig. 2).

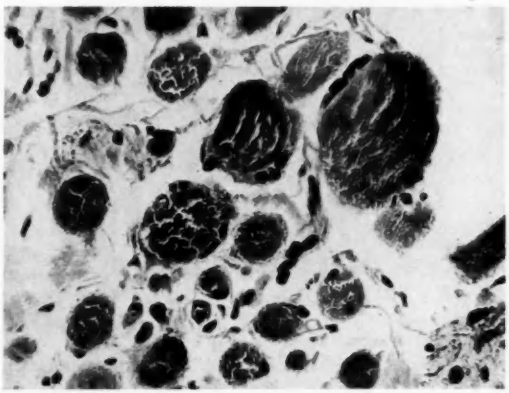

FIG. 2 (*Case* 1).—Right orbicularis oculi muscle. Atrophy of individual muscle fibres. Occasional fibres show hypertrophy. Hæmatoxylin and eosin. × 350.

Right medial rectus muscle.—The portion of the right medial rectus muscle which was examined showed extensive fibrosis. The residual muscle fibres were widely separated by loose areolar tissue, which did not, however, contain any cellular aggregations. The most atrophied fibres showed hyaline and granular degeneration and the sarcolemmal nuclei were pyknotic. Some fibres in longitudinal section were very irregular and had lost all transverse striation. Large fibres were seen in close relation to others showing severe atrophy but their diameter did not exceed that of fibres of a normal control. They also showed some proliferation of their sarcolemmal nuclei and some vacuolar degeneration. The striation of the fibres stained poorly with Heidenhain's iron hæmatoxylin (figs. 3 and 4). Both with this stain and with Holmes' axis cylinder method, numerous nerve bundles were seen in this grossly atrophied piece of muscle. These showed no definite abnormality. There were many fragments of nerve fibres in the fibrous tissue between the few remaining muscle fibres but their termination and nature could not be determined.

As motor units in the external ocular muscles contain only 3 to 6 muscle fibres, it may be more difficult to distinguish a neural from a myopathic atrophy in these muscles. In this case, however, the specific degenerative features were quite distinct from the simple atrophy which follows nerve section, and the identity of the pathological process in the medial rectus with that present in the orbicularis oculi muscle is evident.

Vastus lateralis.—As fascial strips were required for the purpose of the ptosis operation, a portion of the right vastus lateralis muscle was obtained and examined

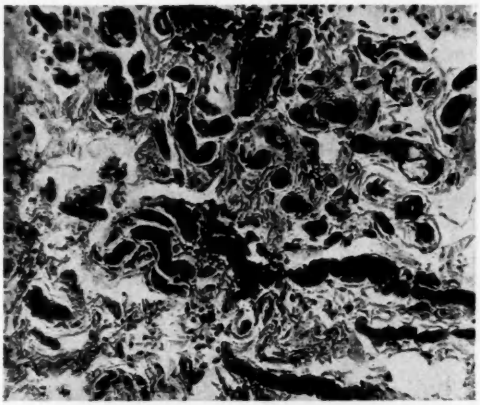

FIG. 3 (*Case* 1).—Right medial rectus muscle. Extensive atrophy of the muscle fibres. Hæmatoxylin and eosin. × 160.

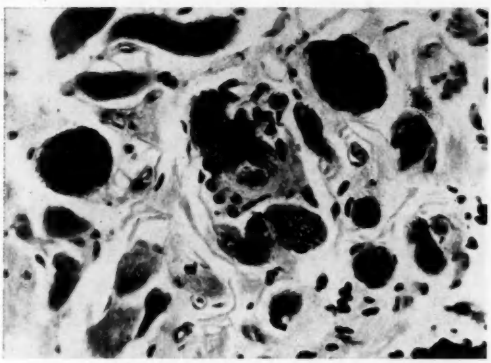

FIG. 4 (*Case* 1).—Right medial rectus muscle. Intense focal degeneration of a large muscle fibre. Hæmatoxylin and eosin. × 400.

microscopically. This showed no gross abnormality but there was definite proliferation of the sarcolemmal nuclei and in places these were arranged in short chains.

Summary.—A man, aged 56, had bilateral ptosis and external ophthalmoplegia of ten years' duration. He also had wasting of some of the facial and masticatory muscles and of the muscles of the neck and upper limbs. A clinical diagnosis of muscular dystrophy was confirmed by histological examination of portions of the right orbicularis oculi and rectus medialis muscles.

Case 2.—R. S., a male aged 45, was admitted to King's College Hospital on November 28, 1949, under Dr. Bruce Pearson.

Twenty years previously, he had suddenly lost the sight of his right eye, due to thrombosis of the central retinal artery and about the same time both his upper

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eyelids began to droop. This symptom slowly progressed for two to three years but thereafter remained unaltered. He has never been aware of any restriction of his ocular movements. During the past two years he has complained of increasing weakness of his upper and lower limbs but he has been able to continue his work as a clerk up to the time of his admission to hospital.

He has suffered intermittently from ulcerative colitis since 1929 and in 1947 his sigmoid colon was resected because of chronic large bowel obstruction. There was nothing relevant in the family history.

On examination there was bilateral symmetrical ptosis and when looking straight ahead, two-thirds of each pupil were covered. The palpebral fissures were 7 mm. in width (fig. 5) and widened to 9 mm. on looking upwards. All ocular movements

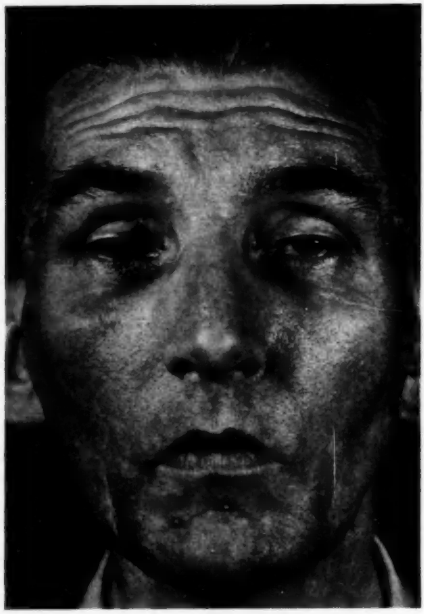

FIG. 5 (*Case* 2).—Patient is looking straight ahead.

were limited and the eyeballs could be moved only 10 degrees in any direction from the central position. There was no strabismus. The pupils were equal in size, regular and showed normal reactions to light and on accommodation. The forehead was constantly wrinkled and the eyebrows were a little raised. The orbicularis oculi muscles were wasted and very weak, though the eyes could just be closed. The frontalis and other facial muscles showed moderate weakness. The patient was unable to smile but could press his lips quite firmly together.

There was slight wasting and weakness of the upper trapezii and muscles of the neck, while the sternomastoids were markedly reduced in bulk. The deltoids, spinati and serrati anterior were a little weak but the pectorales were normal. The biceps and triceps were little affected but the flexor and extensor groups of forearm muscles showed moderate wasting and weakness. Wasting of the small muscles of the hands was less marked but definite. The trunk muscles were normal. In the lower limbs, the flexors of the hips were weak and the quadriceps showed definite wasting and

weakness. The other muscles were normal. The tendon reflexes in the arms and legs were elicited only with difficulty. In all other respects the nervous system was normal on examination.

The blood picture, Wassermann reaction, X-rays of skull and chest were all normal. There was no response to neostigmine.

A small portion of the right deltoid muscle was removed for histological examination. Sections of this muscle presented a compact appearance and showed no gross atrophy or increase in interstitial fibrous tissue. The fibres on the whole appeared somewhat larger than normal, many having a diameter of 74 μ while some were as large as 92 μ. Scattered fibres showed well-marked dystrophic changes with granular and vacuolar degeneration and an increase in the number of sarcolemmal nuclei. These changes affected only portions of the fibres and were at times confined to the sarcoplasm immediately beneath the sarcolemma. Only occasional atrophied fibres were seen. Many of the fibres when stained with Heidenhain's iron hæmatoxylin showed poor striation, while those obviously degenerated, presented a curious granular appearance. In view of these findings, it was considered that there could be no doubt that the general and ocular muscle affection was myopathic in nature.

Summary.—A man aged 45 years had suffered from ptosis for twenty years. An incomplete external ophthalmoplegia had developed unnoticed by the patient. Weakness and wasting of the neck, upper and lower limbs had been present for two years. A diagnosis of muscular dystrophy was confirmed by microscopical examination of a portion of the right deltoid muscle.

Case 3.—C. N., a male, aged 44, was admitted to King's College Hospital on March 27, 1948, under Mr. Keith Lyle. He complained of double vision which commenced in June 1946 and slowly became worse. He became aware of drooping of the left upper eyelid about the same time. He had noticed no restriction of his ocular movements and had no other symptoms. There was nothing relevant either in the patient's previous medical history or in his family history.

When examined in March 1948 there was slight ptosis of the left upper lid. He had diplopia when looking in all directions, the greatest separation of the images occurring on looking downwards and to the left. Clinically, only slight weakness of both internal recti was evident but examination with the Hess' screen indicated that generalized slight weakness of all the ocular muscles was present. The pupils were equal in size, regular and reacted normally to light and on accommodation. There was a little weakness of both orbicularis oculi muscles but the eyes could be closed easily. The remaining facial muscles were normal. The sternomastoids were thinner than normal and were weak. No other abnormal physical signs were found in the nervous system.

The blood Wassermann reaction, X-rays of skull and the cerebrospinal fluid were all normal. There was no response to neostigmine.

On May 31, 1948, Mr. Keith Lyle resected a portion of the left superior rectus muscle with some improvement in the diplopia. On June 9, 1948, a right superior rectus recession under Maddox rod control was performed, as a result of which the diplopia was abolished in the primary position.

The patient was seen again on April 19, 1950. He complained of occasional diplopia when looking to right and left but not when looking straight ahead. The ptosis of the left upper lid was a little more marked but the right upper lid remained normal in position. The restriction of ocular movements was more obvious and some limitation of lateral deviation of each eye was now evident, in addition to the limitation of inward movements which had previously been noted.

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The weakness of the orbicularis oculi and sternomastoid muscles showed little change. No other muscles were affected and all tendon reflexes could be elicited easily.

The portion of the left superior rectus muscle which was removed at operation was examined microscopically. It proved to be a tiny fragment of fairly dense structureless tissue staining a light pink in the Van Gieson preparation. It contained some fragments of yellow-staining muscle fibres in which a few sarcolemmal nuclei could be identified. It was concluded that the portion of tissue examined came from the tendinous insertion of the muscle. The few muscle fibres seen showed degenerative changes but no definite conclusion could be formed as to the nature of the pathological process. It was, however, more suggestive of a myopathic than a neural atrophy.

Summary.—A male, aged 44, had ptosis of the left upper eyelid and slowly increasing weakness of the ocular movements for four years. Slight weakness of the orbicularis oculi and sternomastoid muscles was also evident. The pathological changes in the superior rectus muscle as far as they could be examined were suggestive of a muscular dystrophy.

Case 4.—F. C., a male, aged 35, was referred to the neurological outpatient department at King's College Hospital by Dr. Bruce Pearson on March 13, 1950. The patient complained of double vision with drooping of the left upper eyelid since October 1945. In September 1948 the right upper lid also began to droop and this has slowly become worse. He has no other symptoms and there is no family history of ptosis or ophthalmoplegia.

Examination showed bilateral ptosis more marked on the left side. One-third of the right pupil and two-thirds of the left pupil were covered when looking straight ahead (fig. 6). The right palpebral fissure was 8 mm. and the left 6 mm. in width. There was a little restriction of medial deviation of each eyeball and some weakness of the left superior oblique muscle. The ocular movements were otherwise normal. The pupils were equal in size, circular and showed normal reactions to light and on accommodation. His forehead was a little wrinkled but the eyebrows were not raised above the level of the supraorbital ridges. His facies was impassive and there was moderate weakness of both orbicularis oculi muscles. The other facial muscles were normal. No other abnormal physical signs were found. Neostigmine had no effect.

Summary.—A male, aged 35, had suffered from ptosis of the left upper eyelid and diplopia for five years and ptosis of the right upper eyelid for two years. In addition to the ptosis and weakness of medial deviation of both eyes, there was moderate weakness of both orbicularis oculi muscles. The clinical diagnosis was ocular myopathy.

Case 5.—W. F., a female aged 42, was admitted to King's College Hospital on April 3, 1950, under Dr. Macdonald Critchley. She first noticed drooping of her eyelids in 1935 and this symptom progressed up to the time of her admission. At its onset she was also found to be suffering from mild thyrotoxicosis and this was treated by a course of deep X-rays to her neck. In 1939 she first noticed that the ptosis was partially relieved for some minutes when she drank unsweetened lemon juice. There was nothing relevant in her family history.

On examination, there was severe bilateral ptosis, the pupils being almost completely covered when she looked straight ahead (fig. 7). The palpebral fissures were 4 mm. wide. The ocular movements were normal and the pupils reacted briskly to light and on accommodation. There was some wrinkling of the forehead but

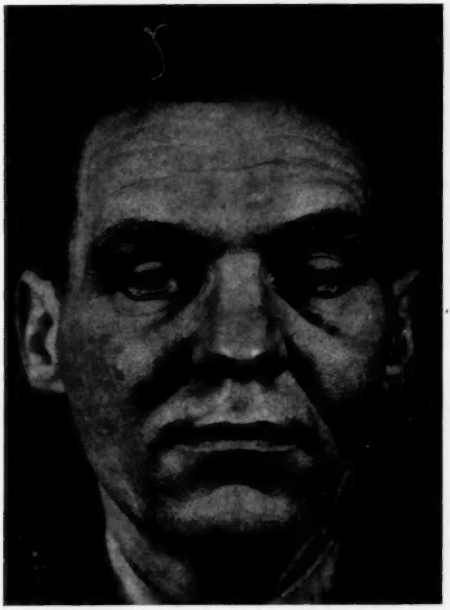

FIG. 6 (*Case* 4).—Patient is looking straight ahead.

FIG. 7 (*Case* 5).—Patient is looking straight ahead.

no weakness of any of the facial muscles. No other abnormal physical signs were found.

The blood picture was normal, the Wassermann reaction negative and the C.S.F. completely normal. X-rays of chest, skull and orbits were normal. There was no response to neostigmine.

Needle electrodes were inserted into the levator palpebræ superioris muscle on either side. Only very weak action potentials were obtained. No denervation potentials were seen. Each muscle was stimulated with currents varying in duration from 0·01 m.sec. to 100 m.secs. but no contraction could be obtained although the current was strong enough to cause contraction of the arm muscles underlying the indifferent electrode.

The swallowing of lemon juice was found to produce definite lessening of the ptosis. The effect commenced about 15 seconds after swallowing the liquid and lasted 3 to 4 minutes (fig. 8). Anything with an acid or bitter taste acted similarly

A B

FIG. 8 (*Case 5*).—A. Normal degree of ptosis. B. Improvement in ptosis one minute after drinking lemon juice.

but only citric acid had such a pronounced result as the lemon juice. The phenomenon was abolished by anæsthetizing the throat with amethocaine. It was probably reflex in nature, the afferent side of the arc being the glossopharyngeal nerve. In view of the pronounced atrophy of the striated muscle fibres of the levators of the upper lids, as shown by the electrical examination, it was concluded that the smooth muscle fibres in the levators were responsible for raising the lids.

On April 3, 1950, Mr. Keith Lyle performed a bilateral Blascovic's operation for correction of the ptosis and small pieces of the levator palpebræ superioris muscles were resected at their insertions into the tarsal plates. A small portion of the left orbicularis oculi was also removed.

Levator palpebræ superioris.—Sections of the levator palpebræ superioris muscles were stained with hæmatoxylin and eosin and with Heidenhain's iron hæmatoxylin. A large amount of smooth muscle was seen but no voluntary muscle fibres were present. This was attributed to the fact that the biopsy specimen of the muscle had been taken near the insertion into the tarsal plate.

Orbicularis oculi muscle.—In sections of this muscle the fibres were more loosely arranged than normal and varied in size from 9–63 μ (normal 20–40 μ) (fig. 9). Small fibres were intermingled with others of maximum diameter. The smallest fibres appeared hyaline and stained deeply with eosin. The larger fibres contained many centrally placed nuclei. There was some vacuolar degeneration round the sarcolemmal nuclei in some fibres.

With Heidenhain's iron hæmatoxylin some fibres stained irregularly and showed in parts a complete absence of striation.

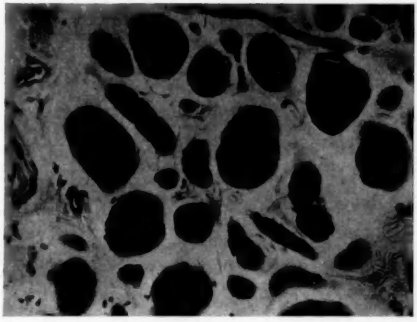

FIG. 9 (*Case* 5).—Right orbicularis muscle. Early myopathic changes.

Summary.—A female patient, aged 42, had suffered from progressive ptosis for fifteen years. Clinically no muscles other than the levators of the upper lids were affected. Histological examination of the left orbicularis oculi muscle, however, revealed changes characteristic of muscular dystrophy. The biopsy material taken from the levator muscles showed only smooth muscle and the striated portion of the muscle was not available for examination.

REVIEW OF THE LITERATURE CONCERNING OCULAR MYOPATHY

Descriptions of cases similar to those recorded in this paper have appeared in the literature over many years and in a few of these, histological examination of biopsy material has been carried out. Fuchs (1890) described 5 cases of isolated bilateral ptosis with atrophy of the upper eyelids. All the patients were females, the age of onset of the condition varying from 15 to 53 years and the duration of symptoms from 3 to 20 years. In 2 of the cases, slight ptosis had probably been present since birth and in one of these there was a family history of ptosis. Fuchs emphasized the peculiar facies of his patients, particularly the elevation of the eyebrows above the supraorbital ridges, and the paper-like texture of the upper lids. In his first case, a woman aged 49, whose symptoms had been present for ten years, he removed a piece of muscle "from the neighbourhood of the levator palpebræ superioris" during an operation for correction of the ptosis.

Fuchs found in the sections of the muscle that many of the fibres were atrophied and that there was an increase in the interstitial fibrous tissue. No definitely hypertrophied fibres were seen but some had local swellings reaching 65μ in diameter. In others there was some irregularity of the sarcolemmal sheaths. The sarcolemmal nuclei were increased in number and were larger and rounder than normal. He concluded that

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his cases represented a previously unrecognized type of primary muscular atrophy restricted to the levators of the upper lids but he also stated that microscopy did not exclude beyond all doubt the possibility that the atrophy was neuropathic in origin. Later however, in his Textbook of Ophthalmology (1923) he refers to the condition as "ptosis myopathica" and from his description of the pathological changes in the muscle, there seems little doubt that the condition was a myopathic degeneration.

Silex (1897) described two cases of "progressive levator paralysis" in elderly females. In one, he removed a piece of the levator palpebræ superioris during an operation for correction of the ptosis and found that microscopically it showed changes typical of progressive muscular dystrophy. There was some increase in fat and fibrous tissue between the muscle fibres which were poorly striated and varied in diameter from 6μ to 110μ. In some fibres, the sarcoplasm was vacuolated and disintegrated but there was only a slight increase in the number of the sarcolemmal nuclei. Silex considered that the cases described by Fuchs were identical with his own and that all were examples of a muscular dystrophy restricted to the levator muscles.

Vollaro (1933) reported the case of a girl aged 19 who had suffered from ptosis since the age of 3 years. Her eyelids covered the upper two-thirds of her pupils and appeared much thinner than normal. No other abnormal physical signs were found. A semilunar strip was excised from each upper eyelid in order to correct the ptosis. The orbicularis oculi muscle appeared to the naked eye to be reduced in thickness. On microscopical examination the bundles of muscle fibres were thinner and more widely separated than normal. The individual fibres varied greatly in diameter and some were reduced to the "very minimum dimensions." Many fibres had lost their striation and had become homogeneous in appearance, staining very deeply. Alongside one another were fibres which were well preserved and others which were "disintegrated and wasted." Some of the fibres contained many nuclei. The skin and subcutaneous tissues of the eyelid also showed atrophic changes. The author thought that the ptosis was the result of a central lesion, probably of the sympathetic nerve supply to the levator muscles and that the changes in the eyelids and orbicularis oculi muscles were trophic in nature. The description and illustrations of the changes in the muscle are similar to those of muscular dystrophy and it appears justifiable to regard this case as an example of ocular myopathy.

Sandifer (1946) described a case of progressive bilateral ptosis and external ophthalmoplegia with weakness of the orbicularis oculi muscles in a man aged 29. No other muscles were affected though the tendon reflexes in the arms were absent. One of the external recti was biopsied

and the microscopical findings in this muscle were considered by J. G. Greenfield to be typically myopathic in nature. The nerve bundles traversing the muscle were normal.

It is clear from the above cases and from Cases 1, 2, 3 and 5, reported in this paper, in all of which pathological examination of the muscles has been carried out, that progressive muscular dystrophy may affect primarily and predominantly the external ocular muscles. Furthermore, there are other cases in the literature which appear to fall into this group, in which the diagnosis of myopathy has been made on clinical grounds alone.

Gowers (1888) described a woman aged 27, who three years previously, began to suffer from bilateral ptosis and external ophthalmoplegia. Later, the facial muscles, particularly the zygomatici and orbicularis oculi muscles, were affected and subsequently wasting appeared in the upper limbs and the muscles of the pelvic girdle. Gowers had no doubt that the diagnosis was muscular dystrophy and thought that the case was of the Landouzy-Déjerine type. The ophthalmoplegia he regarded as an exceedingly rare complication but the myopathic process commenced in the extraocular muscles and the similarity between his case and the first two described in this paper would appear to be close.

The patient seen by Desogus (1923) first complained of ptosis and diplopia when 22 years old. When 31 years of age the facial muscles became weak and wasting appeared in the upper limbs. When examined at the age of 33, there was moderately severe bilateral ptosis with almost complete external ophthalmoplegia. There was a little facial weakness, atrophy of the muscles of mastication and symmetrical wasting of the shoulder and arm muscles. The lower limbs were unaffected. Desogus considered that his patient was suffering from "Myopathie protopathique" and commented that it "was interesting that the ocular muscles were the first to be involved."

Sterling's patient (1929) first suffered from ptosis in infancy. This progressed and when 5 years old, wasting began in both arms. The muscles of the trunk and lower limbs became affected two years later. When examined at the age of 11 years, there was bilateral ptosis with paralysis of upward movement of both eyes. The neck and arms were markedly wasted while the trunk and legs were less affected. The facial muscles were not involved.

Martin (1936) described a man aged 27, who had first noticed ptosis seven years before. Weakness of the face, neck and upper limbs appeared later. Examination revealed a total external ophthalmoplegia, pronounced wasting of the face and neck, including the sternomastoids and wasting of the upper and lower limbs, particularly in the proximal segments.

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Myotonia was absent, but in spite of this Martin thought that the condition was probably allied to dystrophia myotonica. Later, Martin (1939) described two further cases of external ophthalmoplegia which he thought were likely to be myopathic in nature. The first was a girl aged 12 with facial weakness, particularly of the orbicularis oculi muscles, and weakness of the sternomastoids. No other muscles were affected. The second, a boy, showed only a general hypotonia of his musculature in addition to the ophthalmoplegia.

Elliot's (1939) patient was a male aged 38, in whom bilateral ptosis commenced at the age of 28 and limitation of ocular movement six years later. This was followed in the next year by wasting of the neck, shoulders and arms. Generalized facial weakness was also present. The pupillary reactions were sluggish.

Thiébaut *et al.* (1941) reported the case of a male patient aged 23 who first noticed ptosis of the left upper lid when 8 years old. Two years later the right upper lid was affected and he became aware of limitation of his eye movements. Weakness of the shoulder girdle appeared at the age of 12, and of the pelvic girdle when 16 years old. At this age, examination showed considerable ptosis more marked on the left and an almost total bilateral external ophthalmoplegia. The facial muscles were "very little affected," the muscles of mastication were normal and although speech and swallowing were both somewhat difficult, the muscles of the palate, pharynx and larynx appeared normal. The muscles of the neck showed considerable atrophy, the sternomastoids being most affected. There was obvious wasting of the deltoids, spinati and pectorals and less marked wasting of the upper arms. In the lower limbs only the glutei were affected. This case was considered to have "certain features of Erb's type of muscular dystrophy," and it resembles closely our first two cases.

Treacher Collins (1909) reported a case of progressive bilateral ptosis which he compared to those of Fuchs. Although he removed a piece of the levator palpebræ superioris which was atrophic, it was not examined microscopically. Nevertheless he considered that the condition was myopathic in nature.

Other cases which appear to be identical with those already discussed but which are not clearly recognized as myopathic by their authors can also be found in the literature. Bristow (1885) described a male patient aged 53, who first noticed ptosis at the age of 46. When 49 years old, wasting of the shoulders, upper arms and thighs commenced. On examination, there was considerable ptosis, almost complete external ophthalmoplegia, weakness of the masticatory muscles, marked wasting of the muscles of the shoulders and upper arms and slight wasting of

the forearms and thighs. No details of the facial muscles were given. Although the patient admitted that he had had a syphilitic infection, his pupils were normal, the deep reflexes in his lower limbs were retained and "no symptoms or signs of tabes dorsalis were present."

Another case has been reported by McMullen and Hine (1921). When 15 years old the patient noticed slowly progressive bilateral ptosis with difficulty in moving her eyes. When examined three years later by Gordon Holmes, both ptosis and external ophthalmoplegia were nearly complete but no other muscles were affected. Re-examination subsequently by Gordon Holmes revealed definite weakness of the face and of "various muscles of the limbs."

Pelnar (1924) under the title "chronic progressive ophthalmoplegia," described a man aged 40, in whom a slowly developing complete external ophthalmoplegia began when he was 16 years old. His face, and particularly the orbiculares oculi, bulbar muscles, the muscles of his neck and upper limbs, later became atrophied.

A similar case was reported by Poe (1933). A man aged 45 had ptosis from an early age. An almost complete external ophthalmoplegia was noticed when he was 35 years old. The muscles of his face, neck and forearms were weak.

It is therefore clear from the literature and from our own cases, that an important subgroup of progressive muscular dystrophy can be distinguished, which can conveniently be termed "ocular myopathy." Before discussing this condition further, it is necessary to consider whether any or all of those cases described as chronic progressive external ophthalmoplegia, or chronic progressive "nuclear" ophthalmoplegia, are myopathic in nature.

The Question of Chronic Progressive "Nuclear" Ophthalmoplegia

Cases of so-called chronic "nuclear" ophthalmoplegia are characterized by slowly progressive weakness of the external ocular muscles, usually commencing before the age of 30. The condition may advance for many years and in approximately a quarter of the cases the orbicularis oculi muscles are also affected. The conception that this group of cases results from degeneration of the oculomotor nuclei has no pathological basis. It was first put forward by Moebius (1900) who thought that the disease existed in a latent form from birth, and it was repeated by Wilbrand and Saenger (1900) in "Die Neurologie des Auges" (Vol. 1) who first reviewed the condition and collected 32 cases from the literature. With few exceptions, subsequent authors have continued to attribute their cases to nuclear degeneration.

In the appendix to this paper many of the cases of this condition which

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could be traced in the literature have been tabulated. It will be seen that they resemble closely in their general clinical features those examples of ocular myopathy already described, in which the dystrophic process was almost confined to the extraocular muscles. It is improbable that two distinct pathological processes would give rise to such similar clinical findings and while there is clear and definite pathological proof of the myopathic nature of some cases of chronic progressive ophthalmoplegia, there is no satisfactory evidence of an isolated nuclear degeneration as the cause of this condition.

Two cases with post-mortem studies have been published and both are considered by their authors to support the nuclear origin of chronic progressive external ophthalmoplegia. Langden and Cadwalader (1928) performed an autopsy on a female patient aged 84 who had suffered from ptosis since the age of 43 and who showed, nine years before her death, an almost complete bilateral external ophthalmoplegia. No other muscles were affected. They found that the third, fourth and sixth nerve nuclei were well defined but showed a slight reduction in the number of cells present when compared with the nuclei of a young adult. There was some variation in the size and shape of the cell nuclei but only slight chromatolysis. The nerve fibres stained well without evidence of degeneration, though it was considered that the bundles of nerve fibres appeared smaller than normal. Unfortunately the ocular muscles were not examined. The authors considered that the slight nuclear changes were responsible for the ophthalmoplegia and this conclusion has since been widely quoted as evidence of the nuclear origin of chronic progressive ophthalmoplegia. It is difficult to understand how the slight nuclear changes present could be held responsible for the severe ophthalmoplegia. The patient was 84 years of age and the use of a young adult as a control failed to allow for any senile changes that might have occurred. Nor was it considered that the nuclear changes could have been secondary to primary degeneration of the muscles which were not examined. The integrity of the axis cylinders is difficult to understand if indeed the cause of the paralysis was a nuclear degeneration.

More recently a second post-mortem study has been published by Jedlowski (1943). A woman aged 29 had suffered from bilateral ptosis and external ophthalmoplegia for six years before her death from pneumonia. No other muscles were affected. The third, fourth and sixth nerve nuclei all showed some reduction in their nerve-cell content while the remaining cells were wrinkled and irregular in outline. In a number, the nuclei were displaced peripherally and had undergone some degree of pyknosis. The intra- and extra-mesencephalic portions of the ocular nerves were, however, quite normal. The remainder of the brain

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appeared to be normal. The ocular muscles were examined and were stated to be tenuous and somewhat pallid. The microscopic findings are not given in detail and it is merely stated that the muscles showed "simple traces of an atrophy of a secondary type of a not very revealing kind."

In this case, the nuclear changes were much more definite than in that of Langden and Cadwalader, but again the axons were quite normal. Moreover the nature of the muscle changes is not discussed and therefore cannot be evaluated. A number of post-mortem studies on cases of myopathy have been published in which changes, even more marked than those seen in Jedlowski's case, have been found in groups of anterior horn cells supplying the affected muscles (Holmes, 1908; Erb and Schultze, 1879; Kollarits, 1901; etc.) In some areas as many as 85 per cent of the nerve cells had disappeared (Holmes, 1908).

In view of the degenerative changes in the nerve cells which occur in some long-standing cases of myopathy, proof of the nuclear origin of ophthalmoplegia must depend on the demonstration that the muscular atrophy is simple and secondary to degeneration of the neurone and the possibility of myopathy excluded beyond all doubt.

The only other case of chronic progressive "nuclear" ophthalmoplegia discovered in the literature, in which one of the extraocular muscles was examined histologically, was described by Giardini (1948). The patient was a man aged 40 who for twenty years had suffered from slowly progressive bilateral ptosis and external ophthalmoplegia. No other muscles were affected. A bilateral Blascovic's operation was done to correct the ptosis and pieces of each levator muscle were removed. Macroscopically they appeared "almost normal." Microscopically, however, the fibres showed greater variation in diameter than normal although no hypertrophied fibres were seen. The thinnest fibres were scattered throughout the muscle bundles and were intermixed with fibres of normal size. Some showed vacuolation and loss of striation, and the sarcolemmal nuclei were increased in number, a few being "lengthened and tenuous." There was no fatty infiltration. Giardini stated that it was difficult to decide whether the atrophy was primary or neuropathic but finally concluded that it was secondary to nuclear degeneration because of the absence of hypertrophied muscle fibres and of fatty infiltration. There is no reference to the state of the nerve fibres in the muscle. As the author himself had doubts as to the nature of the pathological process in this case and as the changes in the muscle could well be myopathic in nature, it cannot be regarded as furnishing any real evidence in favour of nuclear degeneration as a cause of progressive ophthalmoplegia.

It is clear therefore that none of the pathological studies published to

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date provide any convincing evidence in favour of a nuclear origin of chronic progressive external ophthalmoplegia. They are in fact quite compatible with a diagnosis of primary muscular degeneration, and all cases listed in the appendix are considered by us to be cases of progressive dystrophy of the external ocular muscles.[1]

It is to be noted that Collins (1922) when describing a case of chronic external ophthalmoplegia, suggested that it was due to a primary muscle degeneration of an abiotrophic nature. Fuchs (1923) also held this view and suggested that a slowly progressive degeneration of the muscles themselves was a more likely explanation of these cases than a nuclear degeneration. He appears to have regarded external ophthalmoplegia of myopathic origin and ptosis myopathica as distinct entities. This distinction is not made in this paper.

Although there appears to be no justification at present for assuming that a system degeneration of the oculomotor nuclei resulting in a progressive external ophthalmoplegia exists, it is not denied that these nuclei may be involved in degenerative conditions affecting the central nervous system. Thus Marburg (1936) described a case of progressive external ophthalmoplegia associated with a progressive muscular atrophy affecting the face, throat and upper arms which was apparently of neural origin. Walsh (1947) described another case, probably degenerative in nature, in which an external ophthalmoplegia was associated with widespread muscular atrophy and signs of pyramidal tract disturbance. Such cases appear, however, to be extremely rare.

Clinical Features of Ocular Myopathy

If it is accepted that the cases of chronic progressive ophthalmoplegia listed in the appendix are myopathic in nature, a not inconsiderable subgroup of progressive muscular dystrophy is constituted. The clinical features of this group of ocular myopathies are as follows.

The condition may commence at any time from infancy to over 50 years of age. Some cases have been described in which slight ptosis was present at birth (Fuchs, 1890) but subsequently progressed. The majority commence before 30 years of age. In the accompanying diagram (fig. 10) it will be seen that there is a steep falling off in the frequency after the third decade. Males and females are about equally affected. A family history of ptosis or ophthalmoplegia is found in half of the recorded cases.

[1]Since submitting this paper, a case showing progressive ptosis and a severe bilateral external ophthalmoplegia without involvement of any other muscles has been seen in which a diagnosis of progressive muscular dystrophy has been confirmed by examination of a biopsied specimen of the right inferior oblique muscle.

Ptosis is almost invariable but Heller (1928) records a case in which it failed to appear and Stone (1936) another in which the ptosis remained restricted to the left eye. It is nearly always the first sign of the condition, though Jocqs (1893) and Hanke (1895) described patients in whom the ptosis was preceded by ophthalmoplegia. The ptosis may remain isolated for a number of years, as in Gala's case (1931) in whom it was present five

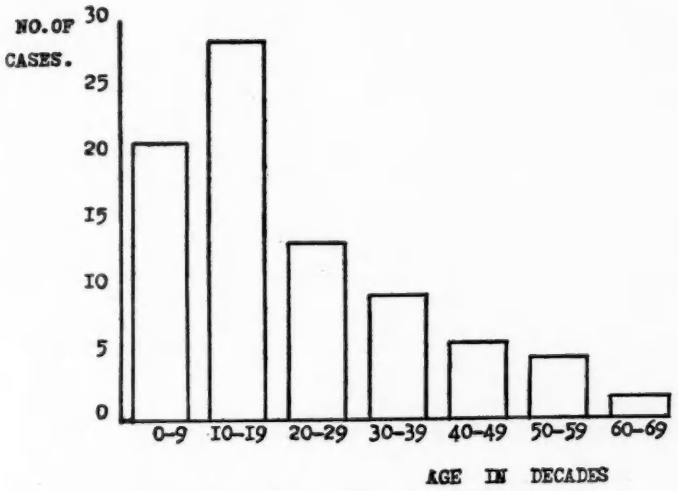

FIG. 10.—Age of onset of ocular myopathy in decades.

years before the onset of ophthalmoplegia, and in Elliott's case (1939) in whom the interval was six years. In an appreciable number of cases, the ptosis and ophthalmoplegia commence simultaneously. The condition may or may not be symmetrical. Occasionally only one eye will be affected for many years. In Fagin's case (1942) the condition commenced in the left eye at 15 years and in the right eye at 39 years of age, while in Altland's case (1909) ptosis of the right eye appeared when the patient was 22 years old, the left eye remaining unaffected for a further twenty years.

The onset and the progress of the condition are both insidious. Cases described as sudden in onset (Abrahamson, 1907, and Beevor, 1887) are to be regarded with suspicion. The condition may continue to advance for thirty to forty years (Fagin, 1942).

Though slight fluctuation in the ptosis may occur in relation to fatigue, marked periodicity and remissions are not seen. The advance of the condition may be halted at any stage either temporarily or permanently. In one of Heller's cases (1928) the condition remained stationary for thirty-

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five years before increasing in severity. Severe ptosis and a total external ophthalmoplegia are commonly found sooner or later.

Diplopia is sometimes an early symptom but is absent in the majority of cases because of the slow development of the ocular palsy and because this is so often symmetrical. In a family described by Faulkner (1939) several members were affected, yet, with one exception, none suffered from diplopia. In the exception, it was the principal complaint. In fully established ophthalmoplegia, a slight divergent strabismus is usual. Even at this stage it is by no means uncommon to find that the patient is quite unaware of his loss of ocular movements, full compensation being achieved by movements of the head. This fact makes an accurate assessment of the duration of the ophthalmoplegia difficult or impossible in many patients.

Pupillary changes are not found in ocular myopathy but a few cases, which in every other respect appear typical, have shown various pupillary abnormalities. The ætiology of these is not always clear but is likely to be unconnected with the myopathy. Meumann (1928) described a family in which 21 members developed ptosis. In all but one the pupils were normal. The exception had fixed pupils—and a history of gonorrhœa. In another family (Dutil, 1892) ptosis with normal pupils appeared in seven members about the age of 50 years. An eighth member developed ptosis at the same age. At first his pupils were normal but later became Argyll Robertson in type. By the age of 66, obvious signs of tabes dorsalis had appeared.

The facies of a patient with severe ptosis and ophthalmoplegia is characteristic and is sometimes referred to eponymously as Hutchinsonian. The forehead is constantly wrinkled in an effort to elevate the lids, the head is tilted backwards and the drooping eyelids give the patient a remarkable sleepy expression. The eyebrows are elevated well above the supraorbital ridges, except in those cases in which the facial muscles are weak. In these, the forehead may be smooth and the eyebrows normal in position. The upper eyelids may become thin and wasted and sink underneath the bony margin of the orbit. In a quarter of the recorded cases various other muscles have been involved and with very few exceptions these have always included the orbiculares oculi. In many, these have been the only additional muscles affected, but in others, the facial involvement has been generalized though more marked in the upper than the lower part of the face. The muscles of mastication are not infrequently affected and almost invariably so by the time the myopathic process has extended to the neck and limb girdles. The temporalis and masseter muscles often show selective wasting.

Involvement of muscles supplied by spinal segments has been found in approximately 10 per cent of cases. All the neck muscles may be weak with considerable wasting of the sternomastoids. The upper trapezii are often affected and the muscles of the shoulder girdle show varying degrees of weakness. The muscles of the upper limbs may also be somewhat wasted and this is usually more obvious proximally than distally. The muscles of the pelvic girdle and lower limbs are less commonly affected but as in one of our cases, they may show changes microscopically, in the absence of clinical wasting. It is uncommon for the patient to complain of any disability affecting the trunk or limbs. Although in the more severe cases, the distribution of the wasting resembles that seen in dystrophia myotonica, the weakness is rarely as great as in this disease, while myotonia, testicular atrophy, cataract and baldness do not form part of the clinical picture. There is no evidence of any relationship between this group of cases and dystrophia myotonica.

Ocular myopathy appears to approach most closely in its general characteristics to the Landouzy-Déjerine type of this disease. It is not our intention to separate it rigidly from other types of myopathy, as the pathological changes found in the muscles are not in any way distinctive.

Summary

(1) Five cases of progressive muscular dystrophy with early and predominant affection of the external ocular muscles are described. It is suggested that the term "ocular myopathy" is applied to these and to other similar cases found in the literature.

(2) The literature concerning chronic progressive "nuclear" ophthalmoplegia is discussed. No evidence has been found to justify the view that these case are due to a systematized degeneration of the oculomotor nuclei. Such cases appear in fact to be examples of ocular myopathy.

(3) The general clinical features of ocular myopathy are discussed and considered distinctive but the pathological changes in the muscle do not differ essentially from those found in other types of progressive muscular dystrophy.

It is a pleasure to thank our colleagues who have allowed us to study their cases. We are also greatly indebted to Professor Magnus for assistance with the pathological studies, to Mr. G. A. Harwood who prepared the sections and to Mr. W. J. Smith who made the photomicrographs.

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APPENDIX

Author	*Sex and age*	*Duration of symptoms (years)*	*Ocular signs*	*Remarks*
von Graefe, A. (1868)	M 40	—	Severe ptosis. Eyes immobile and slightly divergent	This is the first recorded case
Galezowski (1878)	—	—	Bilateral ptosis and external ophthalmoplegia	
Hutchinson (1879)	M 20	2	Considerable bilateral ptosis and external ophthalmoplegia	One of 17 cases reported as chronic external ophthalmoplegia. Others probably syphilitic
Nothnagel (1884)	M 45	30	Bilateral ptosis and partial external ophthalmoplegia	
Strümpell (1886)	M 50	25	Bilateral ptosis and complete external ophthalmoplegia	
Beevor (1887)	F —	6	Considerable ptosis. Severe external ophthalmoplegia	
Birdsall (1887)	M 18	2	Double ptosis more marked on the right with severe opthalmoplegia	
Birdsall (1887)	M 29	4	Marked ptosis and fixed eyeballs	Slight weakness of upper facial muscles
Lawford (1887)	M 60	10	Ptosis and external ophthalmoplegia more marked on the right	
Mittendorf (1887)	M 40	14	Some ptosis, left eye fixed, right almost so	
Davidson (1888)	F 26	8	Double ptosis, divergent strabismus	
Rumschewitz (1888)	M 40	36	Total external opthalmoplegia	
Rumschewitz (1888)	F 12	6	Total external opthalmoplegia	
Cheney (1889)	M 13	10	Almost complete ptosis with severe ophthalmoplegia	
Challin (1890)	—	—	Ptosis and external ophthalmoplegia	
Recken (1891)	F 14	4	Ptosis and external ophthalmoplegia	Slight facial weakness
Lagrange (1892)	—	—	External ophthalmoplegia with ptosis	
Lagrange (1892)	—	—	Ptosis and external ophthalmoplegia	
Dutil (1892)	M 57	12	Symmetrical ptosis	2 other cases in same family

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Author	*Sex and age*	*Duration of symptoms (years)*	*Ocular signs*	*Remarks*
Dutil (1892)	M 66	16	Symmetrical ptosis	7 other cases in same family
Jackson (1893)	— 34	—	Ptosis and severe external ophthalmoplegia	Orbiculares oculi affected
Jackson (1893)	—	—	Ptosis and external ophthalmoplegia	Weakness of orbiculares oculi and of masticatory muscles
Jackson (1893)	—	—	Ptosis and almost complete external ophthalmoplegia	Orbiculares oculi weak
Jocqs (1893)	F 12	11	Rt. ptosis and external ophthalmoplegia	Ophthalmoplegia preceded the ptosis
Hanke (1895)	F 26	? 25	Ptosis with incomplete external ophthalmoplegia	Facial weakness present. Ophthalmoplegia present at an early age, ptosis appeared when 26 years old
Beevor (1895)	F 35	10	Moderate ptosis. Eyes immobile	Orbiculares oculi were very weak
Ayres (1896)	M 38	32	Severe ptosis more marked on the right with complete external ophthalmoplegia	Maternal grandfather may have had same condition
Marina (1896)	—	—	Ptosis and external ophthalmoplegia	
Kunn (1896)	F 55	53	Ptosis and external ophthalmoplegia	
Fragstein and Kempner (1898)	— 47	33	Considerable ptosis and "palsy of both eyes"	Weakness of right upper facial muscles
Taylor (1898)	—	2	Ptosis and external ophthalmoplegia	Weakness of orbiculares oculi and later of the bulbar muscles
Homen (1899)	M 27	12	Ptosis and impaired mobility of eyes	These two cases were twins. No other family history. The upper facial muscles were weak in one only of these brothers
	M 27	12	Ptosis and impaired mobility of eyes	
Davidovits (1900)	M 28	25	Bilateral external ophthalmoplegia	
Koelichen (1904)	F 28	21	Ptosis and external ophthalmoplegia, more marked on the left.	The sternomastoids were also weak
Libensky (1906)	— 25	—	Ptosis and external ophthalmoplegia	
Libensky (1906)	— 29	—	Ptosis and external ophthalmoplegia	
Pasetti and Salani (1907)	—	—	Ptosis and complete external ophthalmoplegia.	A family with 8 cases is described. The onset occurred "in middle life"

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Author	*Sex and age*	*Duration of symptoms (years)*	*Ocular signs*	*Remarks*
Glebowa (1908)	F —	—	Well-marked external ophthalmoplegia	2 cases described with onset at 11 years of age. Other cases known in same family.
Beaumont (1900)	60	10	Ptosis and external ophthalmoplegia	12 cases in one family. In one case only there was weakness of the orbiculares oculi
Delord (1903)	M 66	61	Bilateral ptosis	7 relatives had a similar condition, the onset occurring between 40 and 60 years of age
Thiele and Grawitz (1906)	F 70	—	Isolated bilateral ptosis	Considered to be due to a "senile atrophy of muscles"
Posey (1907)	F 16	—	Severe ptosis and complete ophthalmoplegia	
Altland (1909)	M 51	29	Right ptosis complete, left almost so. Eyes mobile. Divergent strabismus	
Chiarini (1909)	F 24	5	Ptosis and partial ophthalmoplegia	
Chiarini (1909)	F 16	2	Ptosis and partial ophthalmoplegia	
Collins (1909)	F 69	? 30	Severe ptosis more marked on the left	
Uhthoff (1915)	—	—	Ptosis and external ophthalmoplegia	Bilateral facial weakness
Bernhardt (1915)	—	—	Ptosis and external ophthalmoplegia	Weakness of masticatory and pharyngeal muscles
Foerster (1915)	—	—	Ptosis and external ophthalmoplegia	Weakness of facial muscles and possibly of the pharynx
Cantonnet (1920)	M 33	7	Severe ptosis and moderate external ophthalmoplegia	
Fiorenza (1921)	M —	—	Ptosis and partial ophthalmoplegia	Three brothers aged 16, 20 and 30 years are described
McMullen and Hine (1921)	F 18	3	Severe ptosis more marked on the right. Almost total ext. ophthalmoplegia	Weakness of the facial muscles and of "various muscles of the limbs"
McMullen and Hine (1921)	F 12	5	Severe ptosis and external ophthalmoplegia	
Terrien (1921)	F 10	3	Bilateral ptosis and severe external ophthalmoplegia	
Abelsdorff (1922)	F 32	16	Severe ptosis and external ophthalmoplegia	Weakness of orbiculares oculi muscles

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Author	*Sex and age*	*Duration of symptoms (years)*	*Ocular signs*	*Remarks*
Collins (1922)	M 43	18	Almost complete ptosis and external ophthalmoplegia	
Friedenwald (1922)	M 26	12	Severe ptosis and external ophthalmoplegia	Weakness of orbiculares oculi
Friedenwald (1922)	F 19	1	Ptosis more marked on the left. All eye movements restricted	
Stanka (1923)	M 57	32	Ptosis and external ophthalmoplegia	
Stanka (1923)	F 23	4	Ptosis and external ophthalmoplegia	
Cresswell and Hofman (1925)	F 13	4	Marked ptosis	
Ford (1927)	F 17	7	Partial ptosis, almost complete external ophthalmoplegia	Pupils reacted normally to light but sluggishly on accommodation
Heller (1928)	F 72	54	Moderate ptosis and external ophthalmoplegia	Condition stationary for many years but progressed again when 60 years old
Heller (1928)	F 39	2	No ptosis. All eye movements limited	
Langden and Cadwalader (1928)	F 84	41	Severe ptosis and external ophthalmoplegia	Autopsy performed (*see* text)
Meumann (1928)	—	—	Bilateral ptosis	A family in which 21 members were affected
Semeljanskiz (1927)	F 35	23	Ptosis and external ophthalmoplegia	Facial weakness
Semeljanskiz (1927)	F 47	*c.* 37	Ptosis and external ophthalmoplegia	Sister had similar condition
Bertein and Talbot (1929)	— 42	29	Incomplete ptosis with complete external ophthalmoplegia	
Rath (1929)	M 13	8	Ptosis and external ophthalmoplegia	7 other members of family affected. Onset in each case 5–7 years of age
Sterling (1929)	M 11	10	Bilateral ptosis and loss of upward movement of eyes	Weakness of neck, upper limbs, trunk and lower limbs. Some lipodystrophy present. Sister suffered from peroneal muscular atrophy
Gala (1931)	F 23	5	Ptosis and partial external ophthalmoplegia	
Juhász-Schaffer (1932)	M 71	41	Severe ptosis more marked on the left and complete external ophthalmoplegia	

Author	*Sex and age*	*Duration of symptoms (years)*	*Ocular signs*	*Remarks*
Euzière *et al.* (1933)	—	10	Ptosis and external ophthalmoplegia	
Poe (1933)	M 45	? 10	Severe ptosis, ophthalmoplegia almost complete	Weakness of facial muscles and of the upper limbs. Pupils sluggish to light and on accommodation
Vollaro (1933)	F 19	16	Bilateral ptosis	Biopsy made (*see* text)
Takeda (1934)	—	—	Ptosis and external ophthalmoplegia	3 cases, all commencing in childhood
Weinstein (1934)	—	—	Ptosis and external ophthalmoplegia	2 cases described
Stone (1936)	M 28	13	Left ptosis with bilateral external ophthalmoplegia	
Tanobe (1936)	—	—	Ptosis and external ophthalmoplegia	6 cases described
Aguilar (1937)	—	—	Ptosis and external ophthalmoplegia	6 cases in same family described, 3 male and 3 female. Age of onset varied from 17 to 22 years of age
Sui (1937)	M 18	13	Bilateral ptosis and external ophthalmoplegia	
Adamantiadès (1938)	M 14	10	Unilateral ptosis and external ophthalmoplegia	
Dollar (1938)	M 61	6	Progressive ptosis	4 cases in same family. Onset about 50 years of age
Faulkner (1939)	—	—	Ptosis and external ophthalmoplegia	5 cases in same family. 3 males and 2 females
Arcuri and Zanello (1940)	F 46	41	Severe ptosis	
de Farias (1941)	F 13	—	Bilateral ptosis. Left eye immobile, right almost so	
Rose (1941)	—	—	Bilateral ptosis and external ophthalmoplegia	10 cases collected from records of Massachusetts Hospital. Few details given. 5 cases had "weakness of other muscles as well"
Fagin (1942)	M 45	30	Bilateral ptosis with partial ophthalmoplegia	Face described as "stolid"
Jedlowski (1943)	F —	—	Ptosis more marked on the right with ext. ophthalmoplegia	Autopsy performed (*see* text)
Rouques *et al.* (1945)	F 76	31	Bilateral ptosis and external ophthalmoplegia	

Author	*Sex and age*	*Duration of symptoms (years)*	*Ocular signs*	*Remarks*
Cristini (1946)	M 30	12	Ptosis and partial external ophthalmoplegia	Some facial weakness
Walsh (1947)	F 35	5	Moderate bilateral ptosis	Mother and brother had similar condition
Walsh (1947)	— 8	—	Ptosis and external ophthalmoplegia	
Walsh (1947)	M 41	1	Ptosis more marked on the left. Severe external ophthalmoplegia	Slight facial weakness
Walsh (1947)	M 26	10	Severe ptosis and almost complete external ophthalmoplegia	
Walsh (1947)	M 38	2	Left ptosis with bilateral external ophthalmoplegia	
Walsh (1947)	M 33	? 10	Ptosis and external ophthalmoplegia	Ptosis said to have been present since birth. Ophthalmoplegia developed at age of 23
Giardini (1948)	M 40	20	Symmetrical ptosis and external ophthalmoplegia	Biopsy performed (*see* text)

NOTE.—Some of the cases described by Wilbrand and Saenger in "Neurologie des Auges" have been excluded because their aetiology is doubtful. A number of other cases in the literature described by their authors as "chronic progressive external ophthalmoplegia" or "chronic nuclear ophthalmoplegia," have been omitted for the same reason. Unless specifically stated, no other muscles were affected.

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A REVIEW OF THE SYMPTOMS AND SIGNS OF ACOUSTIC NEUROFIBROMATA

BY

C. H. EDWARDS and J. H. PATERSON

Introduction

Until the turn of the last century the accounts of acoustic neurofibromata had been scattered and, with few exceptions, were purely pathological descriptions. Admittedly, some of the more complete papers, particularly that of Jean Cruveilhier, are outstanding for the accuracy of the clinical observations recorded. The last decade of the nineteenth century, however, saw much experimental and clinical investigation which threw light on the functions of the cerebellum and, for the first time, the fuller significance of certain signs of cerebellar disease became evident. The importance of this work in regard to clinical localization of lesions within the posterior fossa of the skull, particularly concerning acoustic nerve tumours, was at once emphasized by the publication of progressively more exact descriptions of their symptomatology. Their clinical picture, in fact, became established and no longer were they pathological curiosities. The surgical attack upon such tumours was stimulated by these clinical advances and the correlation of symptoms and signs with the anatomical findings was extended from the post-mortem room to the operating theatre. In 1917 Harvey Cushing was able to publish his classical treatise based upon a comprehensive study of 30 proven unilateral acoustic neurofibromata, and he clearly defined all the essential features necessary for their diagnosis. Since then their bedside recognition has become a commonplace, but it is nevertheless true that considerable improvement in early diagnosis has yet to be made, for their operative mortality and morbidity is still formidable. The clinical importance of these benign tumours of the acoustic nerve needs no emphasis, for despite the grave results they may lead to, they grow initially from a non-vital structure, the destruction of which occasions only minor disabilities. The object of this paper then is to analyse a large number of case histories in the hope of throwing light on the difficulties that lie in the way of early diagnosis, particularly in respect of unusual features, and at the same time to estimate the strength and clarity of the chronological pattern in the natural history that had first been emphasized by Cushing (1917) and

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which perhaps has been upheld too rigidly as a diagnostic template by other authorities.

Unilateral Acoustic Neurofibromata

We propose to analyse the symptoms and signs recorded in the case histories of 157 patients with unilateral acoustic tumours. These patients were admitted either to the National Hospital between 1921 and 1948 or elsewhere between 1936 and 1948 under Mr. Wylie McKissock. This series does not include all such patients admitted between those years for it was necessary to select those in whom the diagnosis had been confirmed by histological examination at operation or post-mortem, as well as to exclude patients with inadequate case histories. The absence of a second tumour on the opposite side was sometimes verified by autopsy, occasionally at operation and in the remainder was assumed on clinical and radiological grounds.

The symptoms and signs are discussed, together with the findings of other authors, in sections arranged in conformity with the chronological march of events found in the present series.

Table I.—The Incidence of 157 Patients with Unilateral Acoustic Neurofibromata Compared with Other Authors

	Present series	*Cushing*	*Revilla*	*Henschen*
Total	157	30	145	245
Sex: male ...	36%	40%	37%	46%
female ...	64%	60%	63%	54%
Side: right ...	43%	40%	47%	50%
left ...	57%	60%	53%	50%
Average age on admission ...		44·4 yrs.	38·1 yrs.	44·0 yrs.
Age range on admission ...		19–67 yrs.	21–53 yrs.	19–69 yrs.
Mean age at onset ...		(152 pts.)	(27 pts.)	
...		40·8 yrs.	34·1 yrs.	39·0 yrs.

Table Ia.—Age Incidence on Admission and At Onset in 157 Patients With Unilateral Acoustic Neurofibromata

Age in decades	*Age at onset*	*Age on admission*
10–20 ...	4 ...	2
20–30 ...	27 ...	15
30–40 ...	40 ...	38
40–50 ...	50 ...	50
50–60 ...	33 ...	40
60–70 ...	3 ...	12
	157 patients	157 patients

The incidence figures for the present series detailed above show no predilection for sex or side and are in fair accord with those provided by Cushing (1917) Revilla (1947) and Henschen (Quoted by Cushing, 1917), the latter's large number having been collected from the literature up

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to 1915. In Table Ia the age incidences at onset of symptoms and on admission to hospital for the present series are shown. It will be seen that though the extremes of age incidence are wide, the great majority of patients (76 per cent) began to have symptoms between the ages of 30 and 60, and 80 per cent were admitted to hospital for the first time during that period. Unilateral acoustic neurofibromata are rarely encountered therefore outside the middle decades.

The Eighth Cranial Nerve

To avoid confusion we propose to use the term "cochlear symptoms" to cover deafness and tinnitus, the latter being usually considered as due to irritation of the cochlear fibres or their end organs.

Table II.—Eighth Nerve Symptoms in 157 Patients with Unilateral Acoustic Neurofibromata on First Admission to Hospital

Cochlear Symptoms:	
Deafness and tinnitus	82 (52%)
Deafness alone	60 (38%)
Tinnitus alone	2
Without deafness or tinnitus	13 (8%)
Cochlear symptoms initial	103 (66%)
Cochlear symptoms preceding all others ...	67 (43%)
Vestibular Symptoms:	
With vestibular symptoms	66 (42%)
Without vestibular symptoms	91 (58%)
Vestibular symptoms initial	29 (18%)
Vestibular symptoms preceding all others ...	8

Cochlear symptoms.—As is well known, the cochlear symptoms of eighth nerve tumours almost invariably make their appearance at an early stage, and from Table II it will be seen that only some 8 per cent of the 157 patients with unilateral tumours in this series had not complained of deafness or tinnitus on admission to hospital. In 103 of 144 with cochlear symptoms (66 per cent of the total), these were inaugural but it is interesting to note that in 67 instances they preceded all other symptoms by a considerable period of time amounting to ten years or more in 11, between three and ten years in 15, one to three years in 19 and for less than a year in 22 patients.

Tinnitus.—It will be noted that tinnitus usually accompanied deafness, although some 60 patients made no mention of the former complaint. In 82 both tinnitus and deafness were noted, 57 stating that both came on together, 7 holding that the tinnitus preceded the deafness and 18 maintaining that the deafness came on first. However, this variability may well be of little significance as unilateral deafness is frequently not noticed by the patient. A good example of this latter point is provided

by the two patients who complained of tinnitus without deafness, for on admission both were found to be completely deaf on the affected side. When present, tinnitus was usually described as being continuous, and occasionally it constituted a very troublesome complaint. 6 patients, however, described their tinnitus as being intermittent, whilst 12 noted that it passed off when they became completely deaf. In the majority nevertheless it persisted after complete deafness had set in.

Deafness.—In contrast with tinnitus, deafness almost always came on gradually and progressed steadily although the speed with which this took place varied markedly from case to case. In 5 patients deafness of sudden onset was described although a slight pre-existing defect may have escaped notice. Again, several dated their deafness back to a time when they apparently suffered from some infective aural trouble; indeed more than one had had a mastoidectomy on the same side. Whilst there is no evidence to suggest that this is more than a chance association, the matter is of some importance in that it had probably delayed the recognition of the true state of affairs, the slow subsequent decline in hearing attributable to the developing tumour being disregarded until other symptoms made their appearance.

A further complication was that some 7 patients complained of bilateral deafness which was associated with tinnitus in 3; in all 7 these cochlear symptoms began on the side of the lesion, to be noticed at a much later date on the opposite side. In 2 of the 7 the contralateral deafness was clearly due to old middle-ear disease, but in the remaining 4 bilateral deafness was confirmed on examination in 2, the deafness noted on the side opposite to the tumour being of a "nerve," or perception type. In these 2 patients there was nothing to suggest that bilateral tumours were present, so the possibility that their deafness was due to a single tumour cannot be ruled out.

Vestibular symptoms.—The term vertigo, as defined by Gowers, should be used to designate "any movement or sense of movement, either in the individual himself or in external objects, that involves a defect, real or seeming, in the equilibrium of the body" (Gowers, 1893). Some 36 patients in this series had symptoms of this order which arose apparently spontaneously or in response to the precipitating factors discussed below. A further 30 patients described attacks of "giddiness" without any sense of movement, but which lead in many instances to marked loss of balance. As, furthermore, these episodes frequently occurred in circumstances similar to those which were responsible for attacks of vertigo in the former group of patients, it is reasonable to suppose that they too were of vestibular origin although theoretically many other factors could be postulated.

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Thus in all some 66 patients (42 per cent) had vestibular symptoms, and as will be seen in Table II these tended to come on later than cochlear symptoms for in only 18 per cent of the total were they initial, compared with the 66 per cent in which cochlear symptoms were inaugural.

There is a general impression that when vestibular symptoms are due to auditory neurofibromata they are usually transient and mild in degree. With this, on the whole, the findings in this series are in agreement, nevertheless 10 patients described their symptoms as being intense and lasting up to half an hour, although one claimed that each bout lasted for two days and was accompanied by frequent vomiting. In 4 patients clouding of consciousness apparently occurred in some of the attacks, in 3 repeated vomiting was noted, and in at least 12 instances loss of equilibrium at these times resulted in them falling to the floor. When the immediate precipitating factors were analysed it became evident that vestibular symptoms most commonly arose on moving the head suddenly either around a vertical or a horizontal axis. In others a sudden change in posture brought on these symptoms and though some gained relief by lying down, at least one patient noticed that lying on the side contralateral to the tumour was likely to aggravate the trouble. In one patient the intense attacks of vertigo apparently lasted up to three hours at a time and were accompanied by a marked throbbing sensation in the affected ear; during this period the patient noted that the contralateral arm became weak, as also did both legs, so that she required support to avoid falling. Since severe vertigo is not infrequently encountered with vascular lesions of the brain-stem—in posterior inferior cerebellar artery thrombosis for example—it is perhaps not too rash to suppose that, in the case just described and probably in some of the others, the vestibular symptoms were due to transient alterations in the blood supply to the adjacent medulla arising through the presence of an expanding lesion in the cerebello-pontine angle, and not as is commonly supposed, to direct involvement of the eighth nerve by the tumour.

TABLE III.—EIGHTH NERVE SIGNS IN 157 PATIENTS WITH UNILATERAL ACOUSTIC NEUROFIBROMATA ON FIRST ADMISSION TO HOSPITAL

Cochlear Signs:		
With total deafness on the side of the tumour	99	(63%)
With partial deafness on the side of the tumour	56	(36%)
With bilateral deafness	8	
Without deafness	2	
Vestibular Signs:		
Patients in whom the caloric responses were recorded ...	106	
Caloric responses abolished on the side of the tumour	88	(83%)
Caloric responses impaired on the side of the tumour ...	16	(15%)
Intact caloric responses	2	

Cochlear and vestibular signs.—The principal findings are set out in Table III and we do not propose to consider them in any detail as the methods employed for investigating vestibular function were not standardized for all the cases in the series. In only one of the two patients in whom hearing was reported as being normal on the affected side on admission to hospital was the examination made by an otologist but it is of some interest nevertheless that this patient is said to have had intact caloric responses on the side of the tumour. This must be an exceptional finding for it will be seen from Table III that in the majority of patients both cochlear and vestibular functions had been abolished on the affected side by the time they came to be admitted to hospital. In 8 patients bilateral impairment of hearing was found on examination; this matter is discussed in detail later on.

A comparison between these findings and those reported by others reveals few large discrepancies. Cushing (1917) noted that in 25 of the 30 (or 83 per cent) in his series, the auditory symptoms were inaugural and that there was a great variation in their duration, the corresponding figure in Revilla's series of 145 unilateral acoustic tumours being 69 per cent (Revilla, 1947) and in Olsen and Horrax's series of 42 patients, 79 per cent (Olsen and Horrax, 1944). Deafness constituted a symptom in every one of Cushing's cases, in all but one in Revilla's and in all but two of Olsen and Horrax; the total of 8 per cent without cochlear symptoms in this present series constituting a higher proportion than that noted by the observers mentioned above. Tinnitus was noted in 70 per cent, 62 per cent, and 54 per cent of those reported by Cushing, Revilla, Olsen and Horrax and in the present series respectively. As regards vestibular symptoms, Cushing noted that whilst sensations of giddiness relieved by recumbency were not uncommon, in only one case was there an early history of definite attacks of vertigo with falling. Revilla noted similar findings to those described in this paper, namely that vestibular symptoms were present in some 41 per cent, half of these describing a rotatory vertigo as opposed to subjective dizziness or loss of balance. Olsen and Horrax stated that vertigo was "conspicuous by its infrequency," being present in only 31 per cent.

With regard to cochlear and vestibular functions, Cushing noted that 7 of his 30 patients showed some preservation of hearing, this being a larger number than those showing some preservation of vestibular function, for out of the 19 instances in which the results of caloric tests were recorded, 15 showed complete and 4 incomplete interference with the caloric responses. Revilla noted that some 86 per cent showed deafness which was complete in 74 per cent and partial in 22 per cent of the total, deafness apparently being bilateral in 5 instances. Vestibular function was recorded as being impaired on the same side as the lesion in 77 of

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the 87 tested, 10 showing no loss of the caloric responses although hearing was undoubtedly affected. Olsen and Horrax noted deafness in 39 of the 41 patients in whom they were able to test hearing, the deafness being of slight degree in only 2. They found the caloric responses unilaterally abolished in every one of the 33 patients in whom this function was examined. However, in considering these reports not only must one bear in mind Cushing's dictum that "absolute deafness is almost as difficult to certify as an absolute loss of the vestibular reactions," but also that the technique used in testing the latter probably varied considerably in the different series, thus accounting for the discrepancies noted above.

The Trigeminal Nerve

Table IV.—Trigeminal Symptoms in 157 Patients with Unilateral Acoustic Neurofibromata

Without trigeminal symptoms ...		...	92 (59%)
With such symptoms ...	...	...	63 (42%)
(*a*) Intermittent pain	4		
(*b*) Paroxysmal pain	7		
(*c*) Numbness ...	45 (29%)		
(*d*) Paræsthesiæ ...	21 (13%)		
Trigeminal symptoms initial ...		...	16 (10%)

Symptoms.—As will be seen from Table IV 59 per cent of the patients had symptoms referable to the trigeminal nerve or its central connexions. Although 20 per cent of the total showed signs of motor involvement of this nerve not one of them had symptoms from it, the symptomatology therefore is purely sensory in this series. The various complaints were grouped under four headings: pain (intermittent and paroxysmal), numbness and paræsthesiæ. Frontal headache, even when circumscribed and unilateral, cannot of itself be included here, we think, as a symptom of trigeminal nerve involvement for it is much too commonly excited by an expanding lesion anywhere within the skull to be of localizing value. The descriptions of the facial pain fell naturally into two groups, those like idiopathic tic douloureux and those quite unlike it. Numbness has been taken to mean a diminution of or an alteration in the response to tactile stimuli made by the patient himself, or that peculiar "frozen" or "stiff" sensation so often present in a part deprived of normal feeling. The word paræsthesiæ covers the multitude of terms such as "pins and needles," used by patients to describe more positive abnormal sensations in the skin. 7 patients had tic-like pain, their description alone being quite typical of true trigeminal neuralgia. In every instance it began in the second or third division of the nerve; occurring in short-lived bouts lasting seconds or minutes, in response to a skin touch over a well-defined area, to cold air or to eating and drinking. It was described

as sharp, shooting, or like electricity; the bouts tended to be grouped into an attack lasting days or weeks; all had well-marked spontaneous remissions of days or weeks or, in one instance, years. One patient had indeed been diagnosed as having tic douloureux some fourteen years before admission by two neurologists who had watched the patient over a number of years without having occasion to alter their view. This is the only instance, however, in which we had good evidence for the absence of other symptoms and some abnormal signs at the time of onset of the pain. In no other instance was the pain the sole initial symptom, although in 4 auditory symptoms were the only precursors. 4 patients had complained of numbness or paræsthesiæ at the same time as the onset of their facial pain. In the 4 with simple intermittent pain the history alone would have served to distinguish it from trigeminal neuralgia, particularly in regard to its temporal qualities. Only one of the 11 with facial pain had this symptom on the side opposite to the tumour, and this was an example of tic-like pain. No patient complained of symptoms referable to an anæsthetic cornea, i.e. neurotrophic keratitis. As would be expected fifth nerve symptoms were only rarely initial (10 per cent) being most commonly second in chronological order.

TABLE V.—TRIGEMINAL SIGNS IN 157 PATIENTS WITH UNILATERAL ACOUSTIC NEUROFIBROMATA

Without trigeminal signs								19	(12%)
With trigeminal signs								138	(88%)
The Corneal Reflex:									
Normal								20	(13%)
Impaired								59	(37%)
(*a*) On side of tumour							57		
(*b*) On both sides							2		
Absent								78	(50%)
Facial Sensation:									
No impairment of pain or light touch								59	(37%)
Hyperalgesia over face (in 1st and 2nd divisions)								1	
Impaired appreciation of pain and light touch								97	(62%)

Sensory modality	*Divisions of nerve*							*Total*
	1 and 2	and 3	1 and 2	2 and 3	1	2	3	
Pain and light touch	61		6	6	3	0	0	76
Pain alone	7		0	1	1	3	1	13
Light touch alone	4		2	1	1	0	0	8

Motor Signs:									
Weakness present								31	(20%)
Wasting present								5	

Signs.—From Table V the following points are seen: 88 per cent of the total series had signs of trigeminal nerve involvement and of these only one was recorded as having normal corneal sensibility on the side of

the tumour. Only 20 patients in all had normal corneal sensation and, since the 31 with trigeminal motor signs all had skin sensory impairment, it follows that 39 patients had an impaired corneal response as the only fifth nerve abnormality. The findings in this group then agree with the generally accepted notion that this sign is the most sensitive index we have of the presence of sensory loss within the trigeminal territory. This reliability probably depends not only upon the apparent vulnerability of the fibres subserving corneal sensation but on the fact that the clinical test may be a purely objective one, for even when a seventh nerve lesion interferes with the arc of the corneal reflex a sensory impairment is usually obvious in the form of a reduced involuntary response of the normal eye. Although bilaterally impaired or absent in 6 patients it was never a purely contralateral sign. 98 (62 per cent) had other sensory signs also, and it will be seen from Table V that two main points emerge from an analysis of these findings; the great majority showed impairment of both pain and light touch sense, and this loss was most frequently found equally in all three divisions of the nerve. When one or two divisions alone were affected there was a similar and substantial preponderance of simultaneous involvement of both modalities. However, when there was dissociation of these two modalities light touch was the most often spared. In 3 patients only was the impairment contralateral to the growth, although none of them had complained of symptoms on that side. There was evidence of weakness in the muscles supplied by this nerve in 31 (20 per cent) patients, in all of them the weakness was certain and was not assessed on mere muscle bulk alone. In one patient the defect was contralateral to the tumour and he also had an absent corneal reflex on both sides together with impairment of pain and touch sense on the side of the motor involvement.

The exact mechanism causing trigeminal signs in cerebellopontine angle tumours has been a matter for discussion. It is generally agreed that there is a dissociation within the brain-stem of the incoming trigeminal sensory fibres, in such a way that fibres subserving light touch pass to the principal nucleus and that those carrying painful and thermal impressions end in the nucleus of the descending tract, although recent anatomical observations suggest a dual pathway for light touch. Again there is an anatomical arrangement whereby the pain fibres from the first division pass to the caudal end of that nucleus and from the third division to the cephalic portion. The anatomical and functional pattern of the sensory fibres forming the nerve trunk, however, has been disputed. Frazier (1913) thought that the three divisions were topographically represented in the ganglion and the distal part of the nerve trunk in such a manner that the ophthalmic division could be spared by the resection of the lateral two-thirds of the trunk close to the ganglion. Dandy (1929) as the pioneer in the posterior fossa approach to the fifth

nerve for the relief of tic douloureux, came to the conclusion that the pain fibres from all three divisions occupy the posterior (lateral) part of the nerve close to the pons and claimed good results in avoiding anæsthesia of the cornea by dividing the posterior one-half of the nerve in that position. Stibbe (1939), using monkeys, found that section of the posterior half or so of the nerve near the pons resulted in degeneration of all the fibres forming the descending tract. Carmichael and Woollard (1933), however, found no complete segregation of fibres within the nerve corresponding to the different modalities. If the central dissociation is taken for granted and if most of these observers are correct then it would seem that lesions of the descending tract or its nucleus and of the posterior aspect of the nerve would both result in a similar pattern of dissociated sensory loss. If the responsible lesion, however, commonly lay in the descending tract one would expect frequent evidence of involvement of other intramedullary structures, the lower cranial nerve nuclei or the long tracts for instance. In common with others the patients in this series only rarely showed such evidence. The widespread and undissociated sensory loss found in the majority would tend to support the view that it is the nerve trunk and not the central connexions which is the seat of the causative lesion. If this is true one has to explain the discrepancy between the frequency of sensory and motor signs, the former being three times as common in this series. The theory that the sensory fibres of the nerve trunk separate the motor fibres from the advancing tumour seems unsatisfactory, and it would appear more likely that the explanation lies in the relative invulnerability to pressure or to ischæmia of the motor fibres.

In this series there was no recorded example of neurotrophic keratitis before operation. It seems somewhat remarkable that this complication of an anæsthetic cornea should be so rare before operation and not uncommon afterwards, for at least in some patients pre-operative insensitivity seems complete and the possibility of trauma as great. The exact cause of the condition is still far from being fully understood. Duke-Elder (1939) in his textbook reviews the many theories that have been advanced and finds none of them completely satisfactory. He says that neuro-paralytic keratitis may complicate a lesion anywhere on the trigeminal sensory pathway but is more common, quicker to appear and more advanced with lesions at or below the Gasserian ganglion. It is believed that the changes which take place in the corneal epithelium following its denervation (vasodilatation and œdema) are associated with intracellular metabolic changes which lower the resistance of the part to trauma and are similar, in kind, to corresponding changes in denervated skin. There is apparently no evidence to suppose that an autonomic lesion plays any part. It is possible that a complete facial palsy, rare before operation and not uncommon afterwards, is an important accessory

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factor in allowing trauma to precipitate keratitis, particularly in the weeks following operation. The good effects of tarsorrhaphy would lend support to that view, but our records do not help to elucidate this point.

Comparing our figures with those of Cushing (1917), Olsen and Horrax (1944) and Revilla (1947) the following points emerge. The frequency of fifth nerve symptoms was higher in all the above series than in the present one, varying from 15 per cent to nearly 30 per cent greater. Both Cushing and Revilla noted pain as a symptom, all (11 per cent) of the latter's being qualitatively indistinguishable from tic douloureux and all (13 per cent) of Cushing's being simple intermittent pain. 11 of Revilla's 16 cases with tic-like pain are the part-subject of a further paper (Revilla, 1948) in which he emphasizes the danger of disregarding deafness as an associated symptom of what appears to be trigeminal neuralgia and in which he points out the diagnostic value as well as the therapeutic advantages of a posterior fossa approach for the relief of symptoms. Our figure for the frequency of trigeminal sensory signs agrees closely with all the above observers, and the incidence of a normal corneal reflex is broadly the same for all. However, Cushing found exactly double the frequency of trigeminal motor signs as compared with our 20 per cent, Revilla noting them in only 6 per cent. There is general agreement that occasionally trigeminal symptoms and signs are contralateral to the tumour.

Headaches

It is, of course, to be expected that headaches and head pains of one form or another should feature prominently in the symptomatology of acoustic neurofibromata, especially as the majority of cases show indisputable evidence of raised intracranial pressure by the time they are admitted to hospital. This series provides no exception to this generalization and as will be seen from Table VI 84 per cent of the patients with unilateral tumours complained of headaches. The symptoms constituted an initial complaint in 25 per cent, preceding all others in 12 instances. If the nature of the headache experienced is to provide useful diagnostic information at a relatively early stage, the symptom must be analysed carefully in regard to its time of onset, relationship to other symptoms, site and precipitating causes. In preparing such an analysis, however, due regard must be paid to the accuracy of available information; for instance, not every patient is able to recollect the initial site of pain if more troublesome headaches subsequently ensue elsewhere.

Time of onset of headaches in relation to other symptoms.—The mean duration of headaches constituting an initial symptom was some two years, although the range was wide, extending from three months

TABLE VI.—HEADACHE AND NECK PAIN AS A SYMPTOM IN 157 PATIENTS WITH UNILATERAL ACOUSTIC NEUROFIBROMATA

No complaint of headache	25	(16%)
Headache as a complaint	132	(84%)
Headache as an initial symptom	40	(25%)
—preceding all other symptoms	12	
—total duration of headache as an initial symptom 3 months to 8 years		
Main site of headache as recorded in 111 patients:		
occipital	34	(31%)
frontal	46	(41%)
fronto-occipital	14	(13%)
vertex	9	
fronto-vertical	5	
occipito-vertical	3	
Complaining of sub-occipital or neck pain ...	31	(20%)
—associated with neck stiffness	9	

to eight years. The mean duration of headaches in the total of 111 cases in which the site was recorded was 1·3 years. As will be seen later in this paper the average time of onset of headaches was some 2·3 years from the commencement, headaches coming on at about the same time as cerebellar symptoms (2·5 years), after trigeminal symptoms (1·9 years) but well before the onset of symptoms which suggest a rising intracranial pressure such as failing vision (3·2 years). This relationship infers that headaches are usually due initially to factors other than those responsible for obstruction to the cerebrospinal fluid pathways, although as will be seen, it is often difficult to sort out the various causes in individual cases.

Site and character of headaches.—Table VI shows that when the main site of headache is considered without regard to when that symptom came on, a frontal situation was encountered slightly more commonly than an occipital, in 46 cases as opposed to 34. However, in 14 patients headaches were referred to both the frontal and occipital regions, and in 3 instances to the top of the head as well as to the back. Thus, occipital headaches were noted in 51 out of the 111 cases in which the site of headache was recorded. Occipital headaches alone were noted in 34 instances, taking up a strictly unilateral site on the side of the tumour in at least 8 and a contralateral site in 1 case. In the other 25 the pain was either bilateral or the side concerned was not noted. The pain was usually described as being intermittent, varying from a dull discomfort to a sharp severe pain. It was frequently precipitated or aggravated by sudden exertion or change in posture (especially stooping) and was commonly described as being most severe on waking of a morning. Occasionally the headache radiated forwards from its occipital site to spread into the frontal regions, and sometimes, though not always, this

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radiation was confined to the ipsilateral side. At other times it radiated downwards into the neck and to anticipate the later discussion of suboccipital and neck pains, such a radiation from an occipital site was noted in 7 out of the 34 patients under consideration. In 4 patients with unilateral occipital headache on the side of the neurofibroma the pain was described as a dull intermittent ache felt immediately behind the affected ear; the significance of this symptom will be discussed below.

In 46 cases, as noted above, headaches were mainly frontal in situation, being confined to the ipsilateral side in 7, referred to the contralateral side in 1 and definitely noted as being bilateral in 11 instances. In the main the pain was rather diffusely referred to a frontal region although in several instances it was described as a sharp, shooting or throbbing pain which was relatively restricted to a retro-orbital site. Otherwise the character of the headache was similar to that experienced in the occipital regions, whilst precipitating factors were likewise of the same order. Radiation of frontal head pains backwards was not noted but in 14 of the 46 patients suboccipital or neck pains were an accompanying feature and in one case the frontal ache had latterly been associated with a pain behind the ear on the side of the lesion.

Simultaneous frontal and occipital headaches were recorded in 14 instances, in 2 of which the frontal pain was confined to a retro-orbital site. In one the pain was entirely ipsilateral and in another it was bilateral in distribution. An associated suboccipital pain was noted in only one case. Vertex headaches were noted in 17 altogether, the headache being confined to that region in 9 cases but involving the adjacent frontal and occipital regions in 5 and 3 instances respectively. In one case the vertex pain was described as spreading down over the face and into the jaw; the significance of this observation will be discussed later on. In 3 instances suboccipital pain was noted in addition to the vertex headaches.

Suboccipital and neck pains.—31 patients (20 per cent) in this series complained of pain in the suboccipital region or in the back of the neck; commonly this pain was associated with headaches elsewhere. In most cases the pain was not strictly located to either side although in 3 it was described as being limited to the side of the tumour. In 4 instances such a pain was apparently unassociated with any other head discomfort save that one case in addition complained of a severe and constant sense of pressure located just behind the affected ear. The site of the associated headache was recorded in 25 of the remaining 27 patients, and was referred to the frontal, occipital, vertex and fronto-occipital regions in 14, 7, 3 and 1 cases respectively. The onset of suboccipital or neck pain coincided with headaches elsewhere in the majority although in 3

patients the former preceded the latter by a mean period of approximately one year, whilst in 5 suboccipital and neck pains followed on the onset of headaches by some six months on the average.

Suboccipital and neck pains were precipitated by much the same factors as those noted for headaches, namely, a sudden change in posture, straining, sudden rotation of the head on the neck and the like; not infrequently the patient woke in the night with a pain in the neck or noted that it tended to be troublesome early in the morning. Similarly, neck pains were most frequently periodic in character, a short attack of pain coinciding in onset with an exacerbation of the headache. It is perhaps of interest to note that in one case pain in the neck was brought on by factors which caused a transient accentuation of tinnitus referred to the affected ear. Again, in 9 the neck was described as feeling stiff when pain in that region became troublesome.

Duration of headaches.—A question of some importance can now be posed, namely, is there any one common site to which early head pains are likely to be referred? If this question could be answered in the affirmative one might suppose that early headaches would then be due to local factors concerned with the expanding tumour in the cerebello-pontine angle rather than to more distant factors associated with a rising intracranial pressure. It has already been noted that occipital headaches were recorded in 51 out of 111 patients; the average duration of these headaches was 1·8 years, regardless as to whether they were or were not accompanied by pain in the frontal or vertex regions. When frontal headaches alone were recorded the average duration was 0·9 year. These figures suggest that early head pains caused by unilateral acoustic neurofibromata are most frequently referred to the occipital region; they are set out in Table VII.

TABLE VII.—HEADACHES IN 111 PATIENTS WITH UNILATERAL ACOUSTIC NEUROFIBROMATA IN REGARD TO THEIR SITE, DURATION AND ASSOCIATION WITH VOMITING

Site of Headaches	*No. of Patients*	*Mean duration of headaches*	*Associated with vomiting*	*Mean duration of vomiting*
Occipital	34	1·8 yrs.	8	0·9 yr.
Frontal	46	0·9 yr.	15	0·6 yr.
Fronto-occipital ...	14	1·9 yrs.	5	1·0 yr.
Vertex	9	1·3 yrs.	4	0·3 yr.
Fronto-vertical ...	5	0·6 yr.	3	0·3 yr.
Occipito-vertical ...	3	0·5 yr.	2	9·3 yrs.
Total with occipital headaches ...	51	1·8 yrs.	15	0·8 yr.
Total	111	—	37	—

It is, of course, impossible in retrospect to ascertain at what point in the progress of symptoms the intracranial pressure rose above normal

levels; no one symptom points unequivocally to this complication and it is common knowledge that an intracranial tumour may give rise to papillœdema without causing headache, vomiting or failing vision. The latter is far too unreliable a pointer, whilst vomiting is not always due to a raised intracranial pressure. From Table VII it will be gathered that 37 of the 111 patients noted vomiting as a symptom, but of these 8 showed no objective evidence of raised intracranial tension on admission to hospital. In the main, however, it is probably fair to state that when vomiting ensues in the march of symptoms it is associated with factors which have already caused this important complication. If this premise be granted it may well be significant that whereas the mean duration of vomiting was almost the same in those with occipital or frontal headaches (0·8 year and 0·6 year respectively) the mean duration of headaches prior to the onset of vomiting was about one year for occipital headaches as opposed to 0·3 year for frontal head pains. In other words occipital headaches alone or in association with pain elsewhere tend to come on earlier than exclusively frontal pains, and are present for a longer period before symptoms suggesting a rising intracranial pressure make their appearance.

Duration of suboccipital and neck pains.—As has already been noted such pains are present in about 20 per cent of the patients in this series; their mean duration was some 1·2 years with an overall range of from one month to four years, regardless as to whether they constituted the only complaint of pain in the head and neck or were associated with headaches elsewhere. In 13 instances such pains were associated with vomiting which had been present on an average for some 0·9 year before admission. Thus it will be seen that suboccipital and neck pains came on neither conspicuously early nor late in relation to the onset of headache, whilst their presence was no more indicative of a raised intracranial tension than were pains over the head elsewhere.

The findings of other observers.—Cushing (1917), on the subject of headaches in acoustic neurofibromata, wrote as follows: "Though a diffuse, unlocalizable cephalalgia may occur, the early discomforts from which the majority of these patients suffer are less often described as headaches than as paroxysmal pain, more often on the side of the lesion, sometimes frontal, sometimes occipital, but apt to spread from back to front, or occasionally in the reverse direction . . . and a more or less severe boring retro-orbital pain is often complained of." He too noted that soreness or stiffness in the neck on stooping and straining was not an uncommon complaint, which was often more troublesome at night or in the early morning hours, whilst he went on to say that as the growth enlarged the pain became worse, being associated with extreme

tenderness of the suboccipital muscles (usually on the side of the lesion) which led to a protective tilting of the head. Revilla (1947) noted headaches in some 68 per cent of his patients, the complaint constituting an initial symptom in 12 per cent. He stated that the ache was mostly localized to the occipital region, in a half of them tending to radiate to the homolateral frontal region. At times the pain was described as a suboccipital discomfort or referred to a region just behind the affected ear. Revilla stated that on an average acoustic symptoms preceded the onset of headaches by 3·3 years. Olsen and Horrax (1944) noted that headaches were present in 81 per cent with an average duration of some thirteen-and-a-half months. They noted that all patients without trigeminal symptoms had headaches for only a short time or not at all, conversely they found that patients without headaches had trigeminal symptoms for six months or less with one exception. As in addition they found the duration of the two complaints was relatively similar in 81 per cent, they inferred that headaches were less significant of increased intracranial presure than of encroachment on the sensory root of the fifth cranial nerve.

The mechanism of headaches.—As had been seen, in the majority headaches come on at a stage when the intracranial pressure is still probably normal, such head pains being initially most frequently referred to the occipital region. At this stage they are most likely to be due to traction and displacement of local structures in or near the cerebellopontine angle, including the internal auditory and basilar arteries, the inferior surface of the transverse sinus, the dura in the region of the internal auditory meatus, and the ninth and tenth cranial nerves which at operation are frequently found in close relation to the lower pole of the tumour. In 8 patients in this series pain was noticed in or immediately behind the ear on the side of the neoplasm; this site for pain has been described by others and at least two mechanisms have been suggested. H. G. Wolff (1948) on the basis of his experiments regards it as attributable to traction on the internal auditory artery or on the dura surrounding the porus acousticus. Brodal (1948), on the other hand, suggests that this type of pain may be due to involvement of the intermediate nerve as it lies between the facial and acoustic nerves. Possibly both factors are responsible. Bilateral occipital headaches may arise from traction or displacement of vascular structures on both sides of the posterior fossa consequent on brain-stem distortion by the tumour; alternatively distant traction effects attributable to a rising intracranial pressure may be responsible. Both factors can of course operate simultaneously, especially in advanced cases.

It has already been noted that suboccipital and neck pains were

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present in 20 per cent of patients in this series for some 1·2 years before admission. A likely explanation of their production is that provided by H. G. Wolff (1948), namely that they are due to traction on the vertebral and posterior inferior cerebellar arteries, the occipital sinus, or the second and third cervical nerves which, according to some authorities (quoted by Penfield and McNaughton, 1940), contribute sensory fibres to the dura of the posterior fossa. Neck pain may also result from muscle spasm, for not infrequently the head is tilted towards the affected side.

Frontal headaches were commonly noted by patients in this series, but if they were frequently due to involvement of the trigeminal nerve root as is postulated by Olsen and Horrax (1944) and suggested by Revilla (1947), the headaches would surely be associated with pain referred to the second and third divisions of the trigeminal nerve as well, yet this must be a rare finding for in this series this association was noted only once—in the case with vertex pains spreading forwards and downwards over the face. Furthermore, as Cushing pointed out, spontaneous sensory complaints referred to the face more often take the form of paræsthesiæ than pain. H. G. Wolff (1948) found in his patients with intracranial tumours that when headaches were referred to the opposite side to the tumour, the patient always showed evidence of a raised intracranial pressure, and it is felt therefore that while frontal and vertical headaches may in some instances be due to pressure on the trigeminal nerve root, in the majority they are attributable to the more distant traction effects associated with a rising intracranial pressure.

Cerebellar Symptoms and Signs

Cerebellar symptoms.—In the present analysis a symptom of clumsiness, awkwardness or shakiness of a limb was taken to indicate a defect of cerebellar control only when indisputable signs of such a defect were recorded. Similarly a complaint of unsteadiness of gait other than when momentary and accompanied by dizziness, was accepted as evidence of a cerebellar defect. "Giddiness" was assigned to an upset of the vestibular apparatus and has already been discussed.

Table VIII.—Cerebellar Symptoms in 157 Patients with Unilateral Acoustic Neurofibromata

No cerebellar symptoms	36 (23%)
With cerebellar symptoms	121 (77%)
Disordered gait	119 (76%)
Inco-ordination of arms	35 (22%)
Cerebellar symptoms initial	24 (15%)
Cerebellar symptoms preceding all others ...	6

As was anticipated and as can be seen from Table VIII the majority (77 per cent) had cerebellar symptoms. All but 2 of these had some

complaint to make of their gait, this ataxia varying from the mildest sense of instability to the most profound reeling and falling. A few, indeed, on admission were unable to walk at all so severe had their ataxia become. On the whole when once installed this symptom progressed steadily, only in a few was it intermittent. Ataxia of an arm was relatively much less common a complaint (22 per cent) and it would seem that inco-ordination of an arm is less likely to be noticed by the patient than an unsteady gait, for as will be seen from Tables VIII and IX the discrepancy between symptoms and signs is considerably greater for the arm than for gait. Thus 35 patients (22 per cent) complained of inco-ordination of an arm although 100 (64 per cent) were found to have it; on the other hand 92 (79 per cent of those tested) were found to be ataxic whilst 119 complained of unsteadiness of their legs. Why this should be so is not obvious. Perhaps it is that the failure of postural control over the wide field of trunk and legs is a more glaring disability to the patient as indeed it is to the examiner. Doubtless the expert hand balancer would be quicker to refer inco-ordination to the arm. Only 3 patients complained of clumsiness of an arm on the side opposite to the tumour, none complained of both arms being affected. Symptoms of cerebellar upset were initial in 15 per cent with an average total duration of 1·8 years; they preceded all other symptoms in 4 per cent with an average precedence of one year. As will be seen later cerebellar symptoms began, on the average, some 2·5 years after the first symptom, their mean chronological position being fourth or just after the onset of headaches.

TABLE IX.—CEREBELLAR SIGNS IN 157 PATIENTS WITH UNILATERAL ACOUSTIC NEUROFIBROMATA

Gait:		
Patients in whom gait was observed and recorded	116	
Gait recorded as normal	24	(21%)
Gait recorded as disturbed	92	(79%)
Disturbed gait but no inco-ordination of legs observed in supine position	41	(35%)
Inco-ordination of Limbs:		
No inco-ordination of limbs observed	52	(33%)
Inco-ordination of ipsilateral arm and leg	66	
Inco-ordination of ipsilateral arm alone	23	
Inco-ordination of ipsilateral leg alone	3	
Inco-ordination of contralateral arm and leg	2	
Inco-ordination of contralateral arm alone	1	
Inco-ordination of contralateral leg alone	0	
Inco-ordination of all four limbs	5	
Inco-ordination of both arms alone	3	
Inco-ordination of both legs alone	2	

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Nystagmus:			
No nystagmus observed			12 (8%)
Nystagmus present			145 (92%)
Horizontal nystagmus only			79 (50%)
Preponderant to side opposite tumour ...	11 (7%)		
Preponderant to side of tumour	47 (30%)		
No directional preponderance noted ...	21 (13%)		
Unilateral horizontal nystagmus	12 (8%)		
Nystagmus in both horizontal and vertical planes			66 (42%)
Preponderant to opposite side	3		
Preponderant to same side	33		
No directional preponderance noted ...	30		
Impaired Conjugate Movements:			
Horizontally to side of tumour			8
Horizontally to both sides			3
Impaired in all directions			1
Dysarthria:			
Dysarthria noted on admission			19 (12%)

Cerebellar signs.—The majority, 79 per cent of those tested, showed an ataxia of gait of some degree, in most this constituted a tendency to veer to the side on which the tumour lay. A large proportion of those whose gait was not recorded were too ill to allow of the test, but it is presumed that a majority of them would have been ataxic. It is noteworthy that nearly one-half of those with a disturbance of gait showed no inco-ordination of their legs as tested on the bed. This has been ascribed to a lesion wholly or mostly affecting the flocculo-nodular portion of the cerebellum; that part whose afferent fibres are chiefly derived from the vestibular nerves and nuclei. Quite apart from any disturbance of gait 67 per cent of patients showed inco-ordination as tested on the bed, and as would be expected the large majority showed this sign in the limbs on the side of the tumour. Some 6 per cent had bilateral signs, whilst about 1·5 per cent showed inco-ordination confined to the contralateral limbs. It is not difficult to envisage such a deformity of posterior fossa structures as to cause a bilateral cerebellar lesion with corresponding signs on both sides, but it is not so easy to imagine one cerebellar hemisphere on the side of the growth escaping a force sufficient to affect the other side; it is simpler perhaps to suppose an interference with the contralateral blood supply by a smaller force and one acting somewhat unusually, but there is no proof of this. As would be anticipated the majority had both arm and leg affected on the side of the tumour, but when a single limb was involved, it was most commonly the arm. A possible explanation of this is that, with formal testing of single limbs, a small defect in an arm is more striking to the examiner than one in a leg. Put somewhat differently, the leg is at best a relatively

clumsy limb when asked to perform such antics as the heel-shin test, and the result is somewhat more tolerantly appraised. It might be, however, that the arm, a more elaborately co-ordinate part, is more vulnerable than the leg (apart from its function in walking) to divorce from cerebellar control.

Nystagmus.—The frequency and the type of nystagmus found in this series is shown in Table IX. In every instance the nystagmus had those qualities which have been supposed to indicate a lesion of some part of the vestibular pathway, that is to say that the oscillatory movements had both a quick and a slow component, in contradistinction to the ocular or pendular type in which the abnormal movements are more nearly of equal speed and amplitude. Following the usual custom the nystagmus has been named in accordance with the direction of the quick peripheral excursion, as opposed to the relatively slow drift towards the "rest point." As will be seen from Table IX the great majority of patients had nystagmus and this was invariably in a horizontal direction, though 42 per cent had a vertical nystagmus in addition. The common finding was a bilateral horizontal nystagmus; coarse, slow and more remarkable to the side of the tumour, fine, rapid and less striking to the opposite side. 12 patients had nystagmus to one side only, the 7 showing it to the side of the tumour were in no other way unusual and it is possible that some of these at least may have had such a fine and rapid nystagmus to the opposite side as to be missed. Of the 5 with nystagmus only to the side opposite to the tumour one had a defect that might have partially masked oscillations to the other side, namely a sixth nerve palsy. There was no evidence that any of these 5 had been examined earlier than usual in the natural history of the disease. Of the 11 patients showing a preponderance of horizontal nystagmus to the side opposite to the growth, however, no less than four had a marked defect of conjugate ocular movements to the other side. Only 12 patients had no nystagmus, 6 of these showed no other evidence of cerebellar dysfunction but in other respects they were not remarkable. Of the remaining 6, however, 3 had other defects that might have accounted for a nystagmus being absent or overlooked; one had a marked paresis of conjugate ocular movements in all directions, one was completely blind and also had a sixth nerve palsy on the side of the tumour, the third had a complete external rectus muscle palsy on the side of the growth.

Defective conjugate ocular movements.—In 12 patients conjugate eye movements were defective, 8 showing such a disorder to the side of the tumour, 3 to both sides in the horizontal plane, and 1 showing limitation of gaze in all directions. 5 of these patients complained of diplopia, but it is supposed that this had been due to a transient abducens palsy

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which had subsequently cleared up or had become masked by the weakness of conjugate eye movements to the same side. It seems probable that these defects usually arise through impaired cerebellar control of the ocular muscles; Stewart and Holmes (1904) described this finding in both cerebellar and extracerebellar tumours in the posterior fossa and Holmes (1917) also noted it following acute injuries to the cerebellum. This explanation gains support from the finding that in 11 of the 12 patients showing this sign in our series, the nystagmus to the side of the defective eye movements was unusually prominent.

Dysarthria.—19 patients in the series (12 per cent) showed a disorder of speech which was probably cerebellar in origin in the majority although in 5 instances lower cranial nerve palsies, which might have enhanced the disturbance, were also in evidence.

As is well known, in Cushing's somewhat rigid chronological pattern cerebellar symptoms were third to appear (Cushing, 1917), in Revilla's they were second although the latter author emphasized the variability of the sequence in his cases (Revilla, 1947). There is no remarkable difference between the relative frequency of cerebellar symptoms in this group and those of other authors. Cushing made a point of the variability from day to day of his patients' ataxia, with which this series does not fully agree for a striking feature in our case histories was the unremitting nature of the disorder of gait and balance. Both Cushing and Revilla found bilateral inco-ordination of limbs; the former does not discuss this point but it is clear from his published case records that about 20 per cent had bilateral clumsiness of limbs, Revilla found it in 7 per cent, our comparable figure is 6 per cent. Neither of these authors mentions purely contralateral signs of cerebellar disorder, the most perplexing feature. Cushing calls attention, as we have, to the relative frequency of symptoms and signs referred to the legs as compared with the arms. In Cushing's 30 patients there was only one in whom nystagmus was "practically wanting," 28 per cent of Revilla's series were, however, without that sign, our comparable figure being 8 per cent. Revilla's figure seems an astonishingly high one, especially when it is noted that some 14 per cent had inco-ordination without nystagmus. Revilla found no example of vertical nystagmus, an even more striking discrepancy from our figure of 42 per cent. The basis of this difference may rest upon a question of definition; it is the custom in this hospital to designate a nystagmus as vertical whenever the oscillations are produced by conjugate movements of the eyes either upward or downward. The oscillations themselves do not necessarily have to be purely vertical in direction, indeed they rarely are so, for a horizontal or rotary element is commonly seen.

Oculomotor Palsies

Table X.—Oculomotor Symptoms and Signs in 157 Patients with Unilateral Acoustic Neurofibromata

Complaining of diplopia		59 (38%)
Sixth nerve palsy noted		31 (20%)
Ipsilateral to tumour	23	
Contralateral to tumour	1	
Bilateral	7	
Third nerve palsy noted		1
Diplopia present but not analysed		2

Diplopia.—As is well known, diplopia is not an uncommon symptom of acoustic tumours, although usually late in onset. 59, or some 38 per cent, of the patients in this series with unilateral tumours made mention of this complaint. In 5 it constituted an initial symptom, although on an average diplopia appeared only some seven months before the patient was admitted to hospital. Expressed in other terms diplopia was first noticed after a mean period of 3·2 years from the onset of the first symptom; that is at about the same time as symptoms appeared which were attributable to rising intracranial tension. In the majority, however, diplopia when present was not persistent and in some 40 instances it was only noted relatively infrequently. Not uncommonly, having once made its appearance, the symptom passed off, never to recur again.

Sixth nerve palsies.—From Table X it will be seen that 31 patients showed abducens palsies; in the majority (23 cases) these were found on the side of the tumour although in 7 cases bilateral involvement was observed, whilst in another the contralateral sixth nerve was affected. The fact that 8 of the 31 had made no complaint of diplopia was probably attributable to their poor visual acuity.

Third nerve palsies.—In contrast to the 31 patients with sixth nerve palsies, only one was found to show involvement of the third nerve when admitted to hospital.

Abducens palsies frequently constitute a "false localizing sign" in association with intracranial tumours. Collier (1904) explained such palsies as being due to traction on the sixth nerve which resulted from backward displacement of the brain-stem by supratentorial pressure. According to E. Wolff (1928) the responsible factor is kinking of the nerve over the apex of the petrous temporal bone when the brain-stem is driven downwards. However, Sunderland (1948) observes that downwards displacement of the brain-stem is more likely to stretch the nerve initially between the ponto-medullary junction and the point where the nerve pierces the dura in relation to the inferior petrosal sinus—the first two points of fixation of the abducens nerve. Cushing (1917) remarked that in cases with acoustic tumours, it seems improbable that the abducens

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nerve was ever directly pressed upon by the tumour, no matter how much the pons was flattened. He thought that strangulation of the nerve by an overlying vessel was the more probable explanation; in fact in an earlier communication (Cushing, 1911) he had suggested that in some cases the anterior inferior cerebellar artery might be the responsible vessel. However, Sunderland (1948), in his study of the neurovascular relations at the base of the brain, showed that though the sixth nerve was intimately related to the anterior inferior cerebellar artery (the artery passing through the nerve in three of his specimens and deeply grooving the nerve in crossing ventral to it in 16 cases) such a relationship was not usually productive of symptoms. It would seem, therefore, that the last explanation of the comparative frequency with which abducens nerve palsies are found in cases with acoustic tumours is probably incorrect. Additional support for the former views is provided by the finding that in such patients diplopia appears at about the same time as do those symptoms which are due to a rising intracranial tension.

The Facial Nerve

Table XI.—The Seventh Cranial Nerve Symptoms and Signs in 157 Patients with Unilateral Acoustic Neurofibromata

Symptoms:			
Symptoms present			23 (15%)
Complaining of facial spasm			9
Complaining of facial weakness			10
Complaining of impaired taste			10
Signs:			
Total with facial weakness or palsy			99 (63%)
Partial facial weakness noted			93 (59%)
(*a*) Ipsilateral to tumour		89	
(*b*) Contralateral to tumour		3	
(*c*) Bilateral		1	
Practically complete facial palsy			6
Facial spasm observed			17 (11%)
(*a*) Associated with partial facial weakness		13	
(*b*) Associated with a facial palsy		1	
(*c*) Unassociated with facial weakness		3	
Taste examined and recorded			48
Taste recorded as normal			11 (23%)
(*a*) In association with intact facial musculature		5	
(*b*) In association with facial weakness		6	
Taste recorded as impaired			37 (77%)
(*a*) In association with intact facial musculature		8	
(*b*) In association with facial weakness		29	

Symptoms of facial nerve involvement.—In view of the proximity of the facial nerve to the auditory nerve (the motor fibres of the former being separated from the latter by the nervus intermedius of Wrisberg

only) in the auditory canal and cerebello-pontine angle, one would expect facial nerve symptoms to be both common and early in onset. Neither of these expectations are fulfilled, for as Table XI shows only 23 patients in this series had such symptoms, and as will be seen they tend to be relatively late in onset, coming on some 3·3 years after the first symptom. This is even later on an average than symptoms which are directly attributable to a rising intracranial pressure (failing vision and mental retardation). An analysis of these 23 patients reveals that 9 complained of facial spasm on the side of the lesion; the face became periodically drawn up on that side, or frequent twitching of the eyelids, cheek and angle of the mouth was noted. In one case such a symptom was noted from the first but in the main it appeared late, being present on an average for some 1·2 years before admission. Only 7 patients complained of facial weakness, in contrast with the large number who showed objective weakness when examined. They stated that food and saliva tended to dribble out of the angle of the mouth, although in addition 2 had noted latterly that the whole of one side of the face had become all but paralysed. The mean duration of facial weakness was less than that of facial spasm being only 0·8 year. In 10 instances loss of taste constituted a complaint although in only one did it appear to be bilateral, the other 9 patients referring the ageusia to one-half of the tongue. It is not known, however, how frequently this question was put to the patients in this series. The mean duration of this symptom in the 10 instances described was but six months.

Facial nerve signs.—Table XI shows that facial spasm or weakness constituted a common finding on admission. In 93 patients (59 per cent) partial facial weakness confined to the side of the lesion in all but four instances was noted. In 3 the weakness was noted on the contralateral side of the face, and in a further instance both sides were involved in some degree. This facial weakness was not always distributed evenly over the whole side of the face, for not infrequently it was confined to the upper or lower regions. In 6 patients facial paralysis was practically complete, the palsy being noted on the side of the tumour in every case. It is evident furthermore that in 5 of these 6 patients the growth was well advanced in that operation or post-mortem examination revealed acoustic neurofibromata of unusually large dimensions. Spasm of the face on the side of the lesion was observed in 17 instances, but in no case was it very marked, and in only 3 was it associated with facial weakness. In all, therefore, the motor functions of the facial nerve were disordered in 102 or some 65 per cent of the patients in this series. Reference to Table XI shows that taste was examined in 48 instances. As is well known, this modality is difficult to examine accurately at the best of times, but more especially when common sensation over the tongue is coincidently impaired. The results therefore

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have been tabled in two categories, namely normal and impaired taste. 11 of the 48 patients (23 per cent) were reported as showing no loss of gustatory sensibility. It will be seen that in 5 of the 11 the facial motor fibres had also escaped damage and in the remaining 6 in whom some facial weakness was noted on the side of the lesion, it was described as being of slight degree only. Taste was found to be impaired over the tongue on the side of the lesion in 37 of the 48 patients, or 77 per cent of those examined. 29 of these 37 showed facial weakness on the same side.

In Cushing's series of 30 proven cases (Cushing, 1917) some degree of facial weakness was noted in 19 (63 per cent) although in the majority it was inconspicuous. In one case the weakness was apparently bilateral. Cushing emphasized, however, that a great discrepancy could exist between the degree of weakness observed and the amount of distortion of the nerve by the tumour as noted at operation. He cited one case in which the facial nerve on the side of the tumour had been stretched to about five times its normal length and had been thinned out to paper thickness although the only observed evidence of damage hitherto had been a very slight expressional weakness of the lower face. Cushing found spasm of the face to be more frequent than was generally supposed at that time, in 4 of his cases some facial twitching was observed, and in one case a marked spasmodic facial tic constituted the first recorded symptom. He recalled how such rare cases in times past had been thought to have Jacksonian epilepsy. As regards taste, Cushing noted some impairment on the side of the tumour in 16 of his 30 patients, although in 3 of the 16 no coincidental facial palsy had been observed. He took pains to point out, however, that these findings should be accepted with caution in that errors in testing taste might easily be made when common sensation over the tongue was also impaired. Thus he noted that in 4 of the 16 cases with impaired taste this complication was present.

Revilla (1947) noted symptoms involving the seventh cranial nerve in some 16 per cent of his patients, 15 complaining of weakness and 4 of spasm. This percentage is very similar to that obtaining in this series, but the mean duration of symptoms of his patients was much longer than in the present series, being 5·2 years. Objectively, some degree of facial weakness was noted in 70 (48 per cent) of his 145 patients, the disturbance being contralateral in one and bilateral in another. In 17 of the 70 the palsy was apparently complete. Revilla states that although taste was not consistently tested, in 4 instances taste loss was found over the anterior two-thirds of the tongue without any apparent facial weakness on the same side. Olsen and Horrax (1944) found subjective complaints related to the facial nerve to be almost absent in their 42 patients. In 11 cases definite peripheral facial weakness was noted and in a further 15 there was a mild or questionable weakness present.

Contrary to what might be expected on pathological grounds, it is clear that symptoms referable to the facial nerve are not commonly encountered in cases with acoustic tumours, nor do they appear early in the march of events. This state of affairs can be attributed, as Cushing (1917) pointed out, to the considerable resistance shown by the motor fibres of the facial nerve to direct compression by the encroaching neurofibroma.

A review of the recent literature reveals that there is still considerable dispute in regard to the anatomical pathways traversed by the fibres conveying taste sensation from the anterior two-thirds of the tongue to the brain-stem. The subject has been reviewed extensively by others (Schwartz and Weddell, 1938; Rowbotham, 1939) but in brief it will be recalled that the controversy started in the last century when Lussana (1869) on clinical evidence concluded that the taste fibres passed to the geniculate ganglion via the chorda tympani and then on into the pons via the nervus intermedius. Thus Lussana disagreed with Schiff (1867) who stated, on evidence derived from animal experiments, that after reaching the geniculate ganglion via the chorda tympani, taste sensation was conveyed along the greater superficial petrosal nerve to enter the pons with the second division of the trigeminal nerve. Although at present the chorda tympani —geniculate ganglion—nervus intermedius route is perhaps regarded as the usual pathway, removal of the Gasserian ganglion (Cushing, 1903), alcoholic injection of the ganglion (Carmichael and Woollard, 1933) and excision of the greater superficial petrosal nerve (Schwartz and Weddell, 1938) have been shown to cause temporary or permanent loss of taste over the anterior two-thirds of the tongue.

Unfortunately, the information provided by the patients under review in this series does not throw much light on the problem. It will be seen that facial weakness is more commonly associated with impairment of taste than with intact appreciation, as would of course be expected if the nervus intermedius constituted the most important taste pathway. Yet it is evident that in six instances taste was apparently unaffected despite the presence of mild facial weakness. As it seems unlikely that the nervus intermedius itself escaped compression in these cases, one must conclude that either the damage done was insufficient to cause noticeable taste impairment or that an alternative pathway for the conduction of this modality existed which did not traverse this nerve.

The Lower Cranial Nerves and Brain-stem

The glossopharyngeal and vagus nerves.—In 9 per cent of the patients comprising this series palatal pareses were encountered although only 3 of these 14 complained of dysphagia for fluids or solids. In 13 of the 14

TABLE XII.—INVOLVEMENT OF THE LOWER CRANIAL NERVES AND BRAIN-STEM IN 157 PATIENTS WITH UNILATERAL ACOUSTIC NEUROFIBROMATA

Ninth and Tenth Nerves:			
Palatal paresis noted		14	(9%)
Bilateral	13		
Contralateral	1		
Pharyngeal reflex lost		10	(6%)
Bilateral	9		
Contralateral	1		
Eleventh Nerve:			
Weakness of the sternomastoid or trapezius		2	
Twelfth Nerve:			
Lingual palsy present		7	
Ipsilateral	4		
Contralateral	3		
Symptomatic dysphagia		12	(8%)
Pyramidal Signs:			
Recorded on admission		27	(17%)
Ipsilateral	11		
Contralateral	9		
Bilateral	7		
Sensory signs:			
Sensory impairment on trunk and limbs		5	
Ipsilateral	3		
Contralateral	2		
"Brain-stem fits"		1	

there was bilateral involvement. The pharyngeal reflex was lost in 10 instances, the finding being bilateral in 9. Only 2 cases of vocal cord palsy were encountered; doubtless this finding would have been more common if a routine examination of the cords had been made.

The spinal accessory nerve.—This nerve was involved in only 2 patients, weakness of the sternomastoid and trapezius muscles on the side of the tumour resulting. In both instances there was clear evidence of homolateral hypoglossal involvement as well, showing that the finding was probably significant.

The hypoglossal nerve.—In 7 instances damage to this nerve was implied by deviation of the protruded tongue to the side of the tumour in 4 and to the opposite side in 3 patients. In only 1 was definite atrophy of the affected half of the tongue noted, and it is by no means certain that the twelfth cranial nerve was unequivocally affected in all 7 patients for in 3 of them there was definite weakness of the trigeminal musculature on the same side. In such circumstances an apparently asymmetrical protrusion of the tongue might be falsely ascribed to hypoglossal paresis, as Cushing pointed out.

Dysphagia.—Dysphagia was mentioned by 12 patients in this series. As a symptom it was almost always one of the last to arise, having a mean duration of but four months before the patient was admitted to hospital, whilst on average it appeared some 3·8 years after the first symptom. As will be seen, therefore, dysphagia tended to come on after symptoms which suggested a rising intracranial tension.

The brain-stem.—Signs of involvement of the pyramidal pathways were found in 27 patients (17 per cent) on admission to hospital. In the main these were slight, taking the form of alteration in tendon reflexes and plantar response on one side or the other. In 8 instances a mild hemiparetic weakness was noted and a slight spastic diplegia was recorded in a further case. As will be seen from Table XII, these signs were bilateral in 7, homolateral in 11 and contralateral to the tumour in 9 instances. In only 5 patients, however, was any impairment of cutaneous or proprioceptive sensation found below the face. This took the form of mild impairment in pain and temperature appreciation on the side opposite to the tumour in 2 patients, and in a third a similar deficit was noted on the homolateral side of the body. In the 2 remaining patients mild proprioceptive loss was recorded in the ipsilateral hand and foot. One might note that in 2 of these 5 cases there was no demonstrable loss of cutaneous sensation over the face.

Convulsions.—It is well known that in advanced cases a grave complication is that of severe tonic convulsions accompanied by profound disturbances of respiration and circulation. These "cerebellar fits," as Hughlings Jackson named them, are fortunately rare and they were definitely encountered in only one instance in this series. This patient was observed by one of us to have a typical tonic convulsion. Another patient gave a history of frequent epileptiform convulsions for six months prior to admission. He was stuporose and incontinent when he entered hospital and showed bilateral grasp reflexes. Frequent epileptiform convulsions were witnessed before he died in coma without being subjected to an operation. At the subsequent autopsy no cerebellar coning was demonstrated. It is possible that his convulsions (which were not "cerebellar fits") were a complication of a high intracranial tension. In 3 other patients a history of fits was obtained extending back between seven years and twenty months before admission but their nature is not known as they were not witnessed. It is, however, unlikely that they were tonic convulsions.

It is perhaps surprising how infrequently lower cranial nerve palsies are found in association with acoustic neurofibromata in view of the close anatomical relationship between the jugular foramen and the porus acousticus. This infrequency was noted and commented on by Cushing

(1917), and it is also reflected in the figures published by Revilla (1947) and Olsen and Horrax (1944). Again when the degree of brain-stem distortion found at operation or post-mortem on these cases is considered one might well expect that pyramidal and sensory disturbances below the face would be more prominent. Yet Revilla's findings closely accord with our own, for he noted pyramidal involvement in 19·6 per cent and sensory disturbance in but 7 of his 145 cases, involving one or both sides of the body with equal frequency. He thought these findings to be largely confined to advanced cases, but in the present series the incidence of papillœdema in the 27 patients showing pyramidal signs was no higher than in the series as a whole.

We have found no evidence to suggest that in some instances the symptoms and signs referable to the lowest cranial nerves or to the brain-stem so dominated the clinical picture as to lead to a mistaken diagnosis of a vascular or degenerative condition of a bulbar or pseudo-bulbar type, but that this can occur has been suggested by Meyer (1941) who reviewed 5 patients (3 of whom had acoustic neurofibromata) with posterior fossa neoplasms simulating cerebro-vascular disease. In the first of the 3, a man of 58, the trouble began with a rapid onset of headaches, dysphagia and general weakness, but shortly afterwards the symptoms remitted for ten months before returning with the addition of dysarthria. The neurological findings on admission were fairly typical of an acoustic tumour although no evidence of a raised intracranial pressure was found. In these circumstances it is not surprising that the unusual remittent history suggested a vascular disorder although the correct diagnosis was subsequently established. The second case was a man of 55 who, for three and a half years before death, suffered repeated bouts of bizarre dyspnœa and anginal seizures accompanied by signs of acute pulmonary œdema, cyanosis and hypertension. Latterly he became deaf and developed papillœdema. Although he was found at autopsy to have marked cerebral atherosclerosis, it was thought that the attacks of unusual dyspnœa were more likely to be due to brain-stem compression by the acoustic neurofibroma. The third man, who was 56, had a "stroke" four and a half years before he died, followed by weakness of the right side of the face and the left side of the body together with some impairment of hearing. He made a good immediate recovery and was treated for hypertension. Four years later he rapidly developed severe headaches, dizziness, ataxia, dysarthria and failing vision. On admission he was found to have a high blood pressure and to show a spastic paraplegia, extra-pyramidal rigidity of both upper limbs, bilateral grasp reflexes and general confusion in addition to more typical signs. He showed no papillœdema, however, whilst his cerebrospinal fluid pressure on lumbar puncture was within

normal limits. At post-mortem he was found to have an acoustic neurofibroma compressing the right side of the pons and medulla, the right cerebral peduncle and the region of the substantia nigra. His cerebral vessels were considered to show only mild arteriosclerotic changes.

Meyer is of the opinion that there may be a significant relationship between hypertension and infratentorial tumours, possibly through involvement of the vasomotor centres in the medulla by local compression. He found 33 per cent of 64 patients between the ages of 45 and 65 who had acoustic neurofibromata to have a diastolic blood pressure of 100 mm. mercury or over. Of 34 patients in our series who fell into this age group, 15 or 44 per cent showed hypertension according to Meyer's standard. These figures are of course too small to be significant, whilst a fair proportion of normal individuals in this age range must show similar blood pressures. Yet the matter is not of academic interest only, for it is well known that the operative mortality of acoustic neurofibromata is influenced by vascular factors which play an important part during and immediately after the operation (Atkinson, 1949); hence it is not unlikely that the pre-operative blood pressure may prove to be of some importance.

The Effects of Rising Intracranial Tension

Some of the more "distant" effects of a tumour in one of the cerebellopontine recesses have already been discussed; these include abducens nerve palsies and frontal headaches and, as has been noted, they are attributable to distortion and displacement of the brain which is not of necessity associated with an abnormally high intracranial tension. However there remain other manifestations which are more closely related to the latter factor; these include anosmia, impairment of consciousness, and progressive reduction of vision which, as is well known, may progress to complete blindness if unchecked.

Anosmia.—3 patients in this series mentioned anosmia as a symptom, and 8 showed total olfactory loss when examined. All the latter showed well-marked papillœdema in addition.

Impairment of consciousness.—As will be seen from Table XIII the history of 5 patients included some degree of impairment of consciousness, in 4 the complaint was of recent drowsiness, and in 1 of dulling of consciousness progressing to coma. An additional patient was found to be pathologically drowsy on admission. None had had a lumbar puncture previously, and as would be expected, all showed on admission a severe degree of papillœdema with retinal hæmorrhages and exudates. In other respects too they were all advanced cases.

Papillœdema and failing vision.—Table XIII shows that papillœdema of some degree was a finding in 76 per cent of the patients in this series,

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TABLE XIII.—SYMPTOMS AND SIGNS ATTRIBUTABLE TO INTRACRANIAL HYPERTENSION IN 157 PATIENTS WITH UNILATERAL ACOUSTIC NEUROFIBROMATA

Symptoms:		
Complaining of drowsiness or mental obfuscation	5	
Complaining of failing vision	92	(58%)
Complaining of obscurations of vision	27	(17%)
Signs:		
Complete anosmia noted on admission	8	
Drowsy on admission	5	
Comatose on admission	1	
Visual acuity not recorded	23	(15%)
Visual acuity within normal limits	56	(36%)
Visual acuity definitely reduced	60	(38%)
Blind in one or both eyes	18	(11%)
—unilateral blindness 13		
—totally blind 5		
No papillœdema observed on admission	38	(24%)
Papillœdema present on admission	119	(76%)

the comparable figure in Revilla's series (Revilla, 1947) being 67 per cent. We found no significant difference in the incidence of papillœdema in those with long or short total histories. 92 patients (58 per cent) complained of deteriorating vision; all were found to have papillœdema although only 78 had demonstrably reduced visual acuity. Nevertheless 5 were completely blind and 13 had lost all vision in one eye. In only 1 patient was there a visual field defect incompatible with an optic nerve lesion, namely a complete and congruous homonymous hemianopia on the side of the tumour which was not accounted for as an autopsy was not performed. The extreme rarity of such a finding may be taken as evidence that loss of vision in these cases is indeed due to an optic nerve lesion in association with papillœdema and not to vascular damage within the territory of the posterior cerebral artery. 27 patients complained of momentary obscurations of vision; in the majority this symptom was closely associated with sudden changes in head posture, and it is usually explained as being due to transitory ischæmia involving the visual pathways or the retina in association with marked intracranial hypertension. As will be seen visual deterioration rarely constituted an initial symptom, its mean time of onset being 3·2 years after the first symptom. Nevertheless some 10 per cent of the patients in this series noted that complaint as an initial symptom, the figure rising to 15 per cent for those with a total history of not more than two years.

THE CEREBROSPINAL FLUID

The cerebrospinal fluid.—As will be seen from Table XIV a lumbar puncture was performed on 75 patients, the pressure being recorded in 68 instances. 75 per cent had a raised cerebrospinal fluid (C.S.F.) pressure

TABLE XIV.—THE CEREBROSPINAL FLUID IN 75 PATIENTS WITH UNILATERAL ACOUSTIC NEUROFIBROMATA (As Obtained by Lumbar Puncture)

Pressure:		
Number in which the pressure was recorded	68	
Normal pressure (below 170 mm. C.S.F.)	17	(25%)
Increased pressure	51	(75%)
Protein:		
Protein content estimated	73	
Protein content normal	2	(3%)
Protein content raised (0·07 gramme % or above)	71	(97%)

taking the somewhat arbitrary figure of 170 mm. of C.S.F. as the upper limit of normal. From the observations of Smyth and Henderson (1938) it would seem that a normal C.S.F. pressure in the lumbar theca is good evidence of a normal intraventricular pressure. 7 patients were found to have a normal lumbar theca pressure, and therefore presumably normal intracranial tension, with well-marked papillœdema; 4 had a raised lumbar pressure with no papillœdema, the actual figures for these 4 being 300, 300, 260 and 220 mm. of C.S.F. All but one of these 4 had had both frontal and occipital headaches of some severity for a matter of weeks before the lumbar puncture, one of them had nuchal pain and stiffness in addition. These figures serve to remind one that there is no absolute correlation between intracranial pressure and papillœdema and they emphasize our ignorance of the precise mode of production of at least some examples of optic disc swelling in association with intracranial lesions.

TABLE XV.—THE COLOUR OF THE CEREBROSPINAL FLUID IN RELATION TO THE PROTEIN CONTENT IN 51 PATIENTS WITH UNILATERAL ACOUSTIC NEUROFIBROMATA

Protein content (grammes %)	*Colourless*	*Yellow*
0·1–0·2	17	1
0·2–0·3	8	5
0·3–0·4	5	4
0·4–0·5	1	3
0·5 grammes % and above ...	0	7
	31	20

Protein content and colour.—The protein content was estimated in 73 patients. Somewhat differing levels of the normal C.S.F. protein are given by various authorities and it seems that the figure varies a little from one laboratory to another. In 71 patients, however, the protein content was at or above a level of 0·07 gramme per cent, a figure that would be accepted by everyone as abnormally high; in one it was 0·055 gramme per cent and probably therefore abnormal, in the remaining 1 it was 0·02 gramme per cent and certainly normal. The highest figure in

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the series was 1·120 grammes per cent. These figures then are in accord with the usual belief that the C.S.F. protein is almost always raised in the presence of acoustic neurofibromata; they serve to show, however, that on occasion the level may be only slightly raised and even normal. The reason for the high protein in the C.S.F. is still in doubt but from the observations of Henderson and Smyth (1938) it seems unlikely that a subarachnoid block at the foramen magnum plays any part and one must suppose that the excess protein is a product of the tumour itself. In regard to the colour of the C.S.F. Table XV shows what would be expected, namely an increasing frequency of xanthochromia as the protein content rises. It is apparent, however, that protein levels as high as 0·4 gramme per cent may not colour the fluid. Neither the nature of the pigment nor its origin is certainly known but it is probably a product of hæmoglobin or serum protein which reaches the C.S.F. by transudation from the tumour. In no patient in this series were red blood cells found that could not be easily explained by the trauma of the needle nor is there any other evidence here that frank subarachnoid hæmorrhage complicates an eighth nerve tumour. In one patient a positive Wassermann reaction was found in the C.S.F. associated with a positive blood reaction but he showed no clinical evidence of syphilis and in all other respects was a typical case. There were no other abnormal C.S.F. findings; in particular no pleocytosis.

Since the introduction of lumbar puncture evidence has gradually accrued that its performance in the presence of an expanding intracranial lesion can be hazardous. The danger is said to be greater with posterior fossa than with supratentorial tumours and the generally accepted immediate cause of its ill-effects is herniation at the foramen magnum or through the tentorial opening. In a search of the immediate results of lumbar puncture in this series we were unable to find any patient in whom it might be said that this manœuvre had unequivocally precipitated symptoms or signs of this grave complication. Neverthless it is worth considering with care the value of the information obtained, information the use of which must be weighed against the possible danger of getting it. The anatomical diagnosis is dependent upon the history, neurological and otological examination, radiography of the internal auditory meatus and possible air or myodil ventriculography. In the majority the site of the lesion will be narrowed at least to the cerebello-pontine angle and lumbar puncture will do nothing to further localization. In making a pathological diagnosis lumbar puncture seems to be of no help, for both the C.S.F. pressure and protein content are liable to be raised in most of the cerebello-pontine angle lesions that constitute a differential diagnosis of eighth nerve tumour. None of the lumbar puncture findings help in the

least in assessing prognosis or the best operative procedure. It seems to us that lumbar puncture is indicated in but a few patients, namely when the abnormal clinical signs are confined to the eighth cranial nerve, and when radiography of the petrous temporal bone is negative and expert otological examination is lacking or inconclusive. In these circumstances the finding of a raised cerebrospinal fluid protein content will be of considerable diagnostic importance. However we believe that when adjacent nervous structures are unequivocally involved and both the radiological and otological findings uphold the diagnosis, a lumbar puncture is, at least, unnecessary.

A Discussion of the Symptoms Provoked by Unilateral Acoustic Neurofibromata

Duration of symptoms.—In 152 out of the 157 patients in this series, the total duration of symptoms prior to the patients' admission to hospital was recorded, 5 patients admitting to an indefinite duration of many years. The range of total duration was extremely wide for whilst 11 patients claimed a total history of only six months or less (in 4, only three months) a further 11 stated that their symptoms had been present for ten years or more, the longest duration being twenty-two years. Naturally these long periods must be accepted with great reserve, but the very wide range is surely of note. The matter is discussed at greater length below.

Table XVI.—The Duration of Symptoms—Grouping According with the Year of Admission

Year of admission	*Total patients*	*Duration of symptoms* 0–2 *yrs.*	2–5 *yrs.*	*Over 5 yrs.*
1921–35	57	26 (46%)	15 (26%)	16 (28%)
1936–44	49	24 (49%)	18 (37%)	7 (14%)
1945–48	51	22 (43%)	20 (39%)	9 (18%)
Total	157	72 (46%)	53 (34%)	32 (20%)

If the series be arranged in three groups according to the total duration of symptoms (Table XVI) it will be seen that in 46 per cent this period was of two years or less, in 34 per cent between two and five years, and in 20 per cent it was over five years. The overall mean duration of symptoms was 3·6 years, the comparable figure quoted by Cushing (1917) being four years, and by Revilla (1947) 4·9 years.

The order of onset of symptoms.—It will be recalled that Cushing established that "the symptomatic progress of the average acoustic tumour occurs more or less in the following stages, first, the auditory and labyrinthine manifestations; second, the occipito-frontal pains with sub-

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occipital discomforts; third, the inco-ordination and instability of cerebellar origin; fourth, the evidence of involvement of adjacent cerebral nerves; fifth, the indications of an increase in intracranial tension with a choked disc and its consequences; sixth, dysarthria, dysphagia, and finally cerebellar crises and respiratory difficulties" (Cushing, 1917). A study of his monograph, however, makes it clear that the march of symptoms did not take this precise form in every case in his series, of which Cushing was fully aware. This point is emphasized for the reason that some authors have perhaps adopted too rigid an attitude to the question: thus Olsen and Horrax (1944) state . . . "In fact, we too believe that if the complex is not typical, some other type of tumour is likely to be present." On the other hand, Revilla (1947) declared that he could detect no definite pattern in the chronological order of symptoms. He emphasized the great variation in the order in which the symptoms come on and averred that in only 45 instances in his series of 145 patients did the symptoms follow Cushing's pattern.

Clearly it is possible to over-emphasize the practical importance of the order of symptomatic progress especially as the matter hinges to an overwhelming extent on such variable factors as the patient's awareness of his disabilities and his acuteness of memory. We have, however, as a matter of interest formed an assessment of the mean order of onset of symptoms in the 152 patients in whom the total duration was known. This assessment is based on the mean time of onset of symptoms after the inaugural complaints, and is shown in Table XVII.

TABLE XVII.—THE ORDER OF ONSET OF SYMPTOMS

(In 152 Patients with Unilateral Acoustic Neurofibromata in Whom the Total Duration of Symptoms was Known)

Symptom	*Number of patients*	*Mean time of onset of symptom after initial complaint*
Acoustic symptoms	145	0·3 year
Trigeminal symptoms	62	1·9 years
Headaches	130	2·3 years
Cerebellar symptoms	116	2·5 years
Diplopia	62	3·2 years
Other symptoms of raised intracranial pressure	119	3·2 years
Facial nerve symptoms	22	3·3 years
Dysphagia	11	3·8 years

It will be seen that the figures in the right-hand column are of interest in that they reveal both the order of onset of symptoms and also the relative time intervals between them. Thus in regard to the former point the mean order of onset of symptoms is as follows: acoustic symptoms; trigeminal symptoms; headaches; cerebellar symptoms;

symptoms referable to the oculomotor nerves and symptoms of a rising intracranial tension; facial nerve symptoms; and lastly dysphagia. It will be noted that, with the exception of symptoms involving the trigeminal nerve, the order of onset established in this way closely corresponds with Cushing's description of the progress of events.

As regards the time interval elapsing between the onset of each symptom, Table XVII shows that after acoustic symptoms had made their appearance, eighteen months passed on an average before the next appeared. In other words, for nearly half the mean period before the patient was admitted to hospital (3·6 years) acoustic symptoms only were noted. In the next few months trigeminal symptoms (facial pain, numbness or paræsthesiæ) and headaches made their appearance to be followed shortly by disordered cerebellar control. Once more the march was apparently arrested for the greater part of a year before diplopia, symptoms of rising intracranial pressure and facial nerve symptoms (weakness, spasm and impaired taste over one-half of the tongue) were rapidly added to the others. Finally dysphagia, in the majority of cases in which it was present, was the last of the symptoms to appear.

Frequency of individual symptoms.—As few patients with acoustic neurofibromata can be expected to complain of all the main symptoms, it is clearly important to establish the frequency with which they are encountered in this series. This matter has already been discussed under separate headings but it can be conveniently summarized in a table (Table XVIII). Here the cases are grouped in accordance with the total duration of their complaint.

TABLE XVIII.—THE FREQUENCY WITH WHICH INDIVIDUAL SYMPTOMS WERE ENCOUNTERED

Symptom	*Total duration of symptoms*			*Total*
	0–2 yrs.	*2–5 yrs.*	*Over 5 yrs.*	*pts.* (157)
Acoustic symptoms	92%	98%	100%	96%
Headaches	83%	85%	94%	86%
Other symptoms of raised intracranial pressure	78%	74%	88%	78%
Cerebellar symptoms	81%	72%	78%	77%
Trigeminal symptoms	36%	49%	38%	41%
Other cranial nerve symptoms ...	43%	38%	50%	41%
Facial nerve symptoms	11%	19%	16%	15%
Dysphagia	8%	4%	13%	8%

A study of this table reveals that in the majority of patients four main groups of symptoms were rarely absent; namely, acoustic, cerebellar, rising intracranial pressure symptoms, and headaches. These, therefore, can be considered of diagnostic importance. Furthermore it

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will be seen that, in relation to the total duration of the complaint, there is no significant difference in the frequency with which these four groups of symptoms were encountered.

TABLE XIX.—THE FREQUENCY WITH WHICH INDIVIDUAL SYMPTOMS CONSTITUTED INITIAL SYMPTOMS

Symptom	*Total duration of symptoms*			*Total patients*
	0–2 yrs. (72 *pts.*)	*2–5 yrs.* (53 *pts.*)	*Over 5 yrs.* (32 *pts.*)	(157)
Acoustic symptoms	61%	81%	97%	75%
Headaches	37%	21%	6%	25%
Cerebellar symptoms	24%	15%	0%	15%
Other symptoms of raised intracranial pressure	15%	9%	0%	10%
Trigeminal symptoms	11%	15%	0%	10%
Other cranial nerve symptoms ...	10%	2%	0%	5%

The initial symptoms of unilateral acoustic neurofibromata.—A study of Table XIX reveals that although acoustic symptoms, as one might expect, formed the commonest inaugural complaint, they were by no means always present initially. In the series as a whole they were initial in 75 per cent, but in those patients with a relatively short history they were present initially in but 61 per cent. By contrast, when the total duration of symptoms was over five years they were inaugural in almost all instances and, in addition, they then constituted practically the only initial complaint. The explanation of this state of affairs is probably as follows. It has already been shown (*see* Table XVIII) that, regardless of the total duration, the frequency with which cardinal symptoms are encountered remains fairly constant, consequently they will be telescoped together if the total duration be short and dramatic symptoms will then be the more likely to attract initial notice. For example it is easy to conceive that a patient might note the onset of headaches or ataxia before deafness; indeed the gradual onset of the latter often escapes notice altogether. When the total duration of symptoms is spread over many years, however, the march of events is so slow as to allow ample time for the average patient to become aware of his failing hearing before the next main symptom makes its appearance.

Another point of note is that symptoms indicating a rising intracranial pressure (failing vision and obscurations of vision) were amongst the first to be noticed by some 15 per cent of patients with a total duration of symptoms of two years or under and by some 10 per cent of all the cases in this series. These symptoms of a generalized intracranial disturbance may then mask the more significant ones of involvement of the acoustic system and the adjacent cranial nerves. In practice one

can expect that in a fair proportion of cases with a short total duration of symptoms the history as given spontaneously by the patient will differ quite markedly from the more "typical" account provided by patients with slower growing tumours.

The onset of symptoms in relation to the total duration of the case history.—Table XVII, as already indicated, shows the mean order of onset and the relative time intervals between each main group of symptoms in the 152 cases in which the total duration was known. If the whole series be split up, as in Table XVIII and XIX, into three main groups of 0·2 year, two to five years and over five years' duration, it can be shown that in the main not only is there no significant difference in the order of onset of symptoms, but that the relative time intervals between them are approximately the same in each group. It is suggested therefore that the tumour, having once attained such proportions as to give rise to symptoms, usually grows steadily without any significant pause even though its rate of growth varies considerably from case to case. We have found no evidence to suggest, for instance, that in patients with a history extending back over many years the neoplasm frequently ceases to grow for any lengthy period only to resume growth at an accelerated rate.

The Signs Given by Unilateral Acoustic Neurofibromata

The physical signs encountered in this series of unilateral acoustic neurofibromata have already been discussed in some detail, to avoid unnecessary repetition therefore it is proposed to limit this commentary to but a few aspects.

Atypical cases.—It is clear that if any cases in this series merit classification as "typical" examples, such a distinction would have to be based largely on objective manifestations and not on the symptoms recounted by the patient. Of the many signs encountered deafness, cerebellar manifestations and evidence of trigeminal involvement were so frequently observed that any patient lacking but one of these signs can, we think, be regarded as presenting an atypical picture. In this group then can be placed 2 patients from this series who showed no deafness, 6 without any signs of cerebellar inco-ordination or nystagmus, and 19 (12 per cent of the total) in whom no impairment of the corneal reflex or of facial sensation was found. Of the 2 without deafness, 1 showed well marked sensory trigeminal signs, nystagmus and ipsilateral cerebellar inco-ordination of the limbs, and the other though apparently free from trigeminal signs and nystagmus yet showed limb ataxia of a cerebellar type. All 6 patients without cerebellar signs showed an appropriate loss of hearing, and all

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but one showed well-marked trigeminal sensory involvement. Furthermore, 18 of the 19 without trigeminal sensory signs were deaf in some degree, and only 1 patient lacked cerebellar manifestations.

Cardinal diagnostic signs.—On rare occasions, as is well known, the presence of an acoustic tumour has been suspected and confirmed before any structure other than the eighth nerve have apparently been involved, but no examples of such early cases were found in the present series. In fact a study of the figures which have just been presented suggests that deafness, cerebellar and trigeminal sensory signs can be considered to be of cardinal importance in the diagnosis of acoustic neurofibromata. In other words, deafness unassociated with nystagmus, cerebellar inco-ordination or impairment of corneal or facial sensation is unlikely to be due to an acoustic tumour.

Bilateral signs.—The presence of bilateral auditory, cerebellar, and trigeminal signs in 19 of the patients in this series merits some comment in that they might have led to the erroneous assumption that double acoustic tumours were present, although the clinical picture scarcely resembled that commonly given by bilateral neurofibromata as usually only one and never more than two bilateral signs of this order were encountered.

Bilateral deafness was found in 8 patients, one showing bilateral cerebellar inco-ordination and another bilaterally impaired corneal responses in addition. In 3 of the 8 patients deafness on the side opposite to the tumour was probably due to coincidental factors such as middle-ear infection or otosclerosis, and in these instances deafness was more marked on the ipsilateral side. In the remaining 5 patients the cause of the contralateral deafness was not clearly established, but it may be of note that 4 of the 5 were advanced cases and, judging from the findings of others, there is the possibility that their deafness was attributable to the unilateral tumour. Thus Revilla (1947) records 5 instances of bilateral "neurogenic" deafness in his series of 145 patients with unilateral acoustic tumours, with bilateral impairment of the cold caloric responses in 5 of the 87 on whom this test was performed. Cushing noted contralateral impairment of hearing in at least 3 patients in his series of confirmed unilateral acoustic neurofibromata.

Bilateral cerebellar inco-ordination of the limbs requires little comment; it was noted in 7 instances but constituted the only bilateral sign in 6 patients although all save one had advanced manifestations of the disorder. Inco-ordination was definitely more marked on the side of the tumour in 4 and in only 1 patient was the reverse effect noted. Bilateral inco-ordination of this nature has been recorded by other observers and it is not difficult to envisage a large unilateral acoustic tumour growing in the

restricted confines of the posterior fossa and producing contralateral involvement of the cerebellar pathways.

Bilateral trigeminal sensory impairment was recorded in 7 patients in one of whom it was associated with bilateral deafness. Both corneal reflexes were unobtainable in 4 patients, and in 2 of the remainder the corneal response was more markedly impaired on the side opposite to the tumour; in addition in 3 instances contralateral corneal impairment was associated with contralateral hypalgesia and hypoæsthesia over the face. However it is interesting to note that in two of these patients such contralateral signs cleared up following operation. Cushing (1917) found that 4 patients in his series had bilateral corneal anæsthesia with bilateral sensory impairment over the face in 4, and Revilla (1947) records 14 instances in which both corneal responses were impaired, contralateral sensory impairment over the face being found in 4 patients. In explanation of these findings it may be of significance that all 7 patients in the present series were advanced cases. Furthermore, as the contralateral trigeminal signs cleared up following operation in two instances, it seems likely that they were due to reversible vascular factors produced by distortion and displacement of the brain-stem which, in view of the involvement of both light touch and pain modalities in three instances, were probably operative at an extrapontine site.

Bilateral Acoustic Neurofibromata

There were 7 patients in this series with bilateral acoustic neurofibromata, the diagnosis being confirmed at operation in 2 and at post-mortem in 5. 2 patients were female and 5 male. The age on admission ranged from 15 to 31 years, with a mean of 23·6 years, although the mean age at onset of symptoms was 18·7 years for the 6 cases in which the total duration of symptoms was known.

Symptoms.—These do not call for detailed discussion as in the main they closely resemble those given by unilateral acoustic tumours. The mean total duration of symptoms in 6 instances was 3·6 years, with a range of from 2 to 6·5 years. *Acoustic* symptoms were initially present in all 7 patients, being characterized by deafness and tinnitus in 4 and deafness alone in 3; the deafness being bilateral in 4 patients. It is of note that deafness was first noticed in both ears at about the same time in 2 of the latter. Vertigo and tinnitus were not prominent as only 2 patients made mention of this complaint; in neither was it marked whilst in both it was only noticed as a comparatively late manifestation. Cerebellar symptoms were noted by all 7 patients, taking the form of ataxia of gait. In none were these or any other symptoms present initially at the time deafness was first noticed. In 3 patients occipital headaches were noted,

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although in only 2 was this symptom troublesome. It is evident then that headaches were far from conspicuous as a presenting symptom. Only 1 patient had symptoms referable to the *trigeminal nerve*, with the complaint of bilateral numbness of the face of short duration, whilst symptoms referable to the *other cranial nerves* were far from prominent. 3 of the 7 patients had noticed *failing vision* before they were admitted to hospital.

Signs.—Acoustic signs: 5 patients showed bilateral loss of hearing which amounted to complete deafness in 3 instances. The remaining 2 patients showed complete deafness in one ear only, hearing being apparently intact in the other ear. The caloric responses were investigated in only 4 of the 7 patients, but in 3 of these they were abolished bilaterally.

Cerebellar signs were characterized by nystagmus and an ataxic gait in all instances and by inco-ordination of all the limbs in 4 patients. In 2 patients no limb ataxia was observed whilst in 1 the arms alone were affected, and in another there was a conjugate gaze palsy to one side.

Trigeminal signs were noted in all instances in that bilaterally impaired or absent corneal responses were found in 6, the remaining patient showing unilateral loss of the reflex only. Bilateral impairment of cutaneous sensation for pain and light touch was noted in but one instance, although in a further 3 patients some unilateral loss of these modalities over one or more divisions of the trigeminal territory was recorded. Unilateral weakness of the muscles of mastication was observed in 3 instances.

Signs involving the facial nerve: In none of the 7 patients was a complete facial palsy recorded although 2 showed bilateral and 4 unilateral facial weakness. Facial spasm was not encountered in any of the patients. The sensation of taste was investigated and recorded in 3 patients only; in these it was said to have been normal in 1 instance and entirely lost over both sides of the tongue in 2.

The other cranial nerves were involved in 3 patients; 1 showed bilateral loss of the pharyngeal reflex and dysarthria; 1 a unilateral external rectus palsy with unilateral weakness of the tongue; the third having a conjugate vertical palsy, a unilateral palatal paresis, cord palsy and hypoglossal paresis together with a hoarse voice and a gross slurring dysarthria.

Visual acuity and papillœdema: Papillœdema was noted on admission in 5 of the 7 patients, disc swelling being severe in 2. 6 patients showed a variable degree of reduction in visual acuity.

Long tract signs: In four out of the 7 patients, bilateral pyramidal tract signs were present, 3 showing bilateral extensor plantar responses whilst the fourth suffered from a marked spastic tetraparesis. On the

other hand, the sensory system below the trigeminal territory was apparently spared in all instances.

Evidence of generalized neurofibromatosis: 6 of the 7 patients in this series showed clear evidence of neurofibromatosis, the condition being subsequently confirmed by post-mortem examination in 4. The matter is discussed more fully in a later section, but it can be pointed out that by contrast only 3 of the 157 patients with unilateral acoustic neurofibromata showed evidence of this generalized disorder.

Comment.—The symptomatology outlined above calls for little comment. It is perhaps surprising that symptoms and signs of raised intracranial tension were not more prominent by the time the patients came into hospital, particularly as other intracranial tumours (associated with neurofibromatosis) were found in the supratentorial compartment in at least two instances. Thus headaches were troublesome in only 2 of the 7 patients, whilst papillœdema was absent in 2 even though subsequent post-mortem examination demonstrated the presence of large bilateral tumours indenting the brain-stem in both instances. It is possible that traction and distortion of vascular structures which, it is supposed, account predominantly for the headaches in patients with unilateral tumours are less likely to occur when both cerebellopontine angles are occupied by growths. Similarly, in the presence of bilateral acoustic tumours displacement of the brain-stem with consequent obstruction to the cerebrospinal fluid pathways may be less likely to take place, particularly if the tumours are of approximately equal dimensions.

The findings reported by Revilla (1947) on the 6 cases in his series with bilateral acoustic neurofibromata are in the main similar to those presented above. Their average age on admission was 23 years (23·6 years in this series) though the mean duration of symptoms was longer, being 5·2 years as compared with 3·6 years. 3 of his 6 cases showed evidence of generalized neurofibromatosis.

The differential diagnosis between cases with bilateral and those with unilateral tumours has on occasions to be considered, particularly when deafness in the former is limited to one ear or, conversely, is bilateral though the tumour be solitary. In this connexion it will be recalled that 8 of the 157 patients with unilateral tumours showed some degree of bilateral deafness. Apart from the fact that bilateral involvement of the other cranial nerves is naturally more commonly encountered in the presence of double acoustic tumours, the younger age of patients with the latter (with a mean age on admission of 23·6 years as compared with 44·4 years) and the frequency with which they show signs of generalized neurofibromatosis, serve to make the differentiation fairly certain in most instances.

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Acoustic Neurofibromata and von Recklinghausen's Disease

Unilateral acoustic tumours.—The association of bilateral eighth nerve tumours with other manifestations of neurofibromatosis of a central or peripheral form is of course common knowledge. What is perhaps less well known is that more rarely unilateral acoustic tumours may be found in similar circumsances. 3 of the 157 patients in this series with unilateral tumours showed complications of this order; their case histories are briefly recounted below:

(*a*) W. S., male, aged 49. Admitted to the National Hospital in 1928 under Dr. Purdon Martin, complaining of thirty years' deafness in the left ear, ten years' intermittent left facial pain, frontal and occipital headaches with occasional diplopia for one year, and unsteadiness of gait for six months.

On examination.—Early bilateral papillœdema, slight hypalgesia over the left trigeminal territory with impairment of the corneal response, left facial weakness with spasm, impairment of hearing with absent caloric responses in the left ear (normal hearing and calorics on the right), nystagmus and ataxic gait. Numerous subcutaneous neurofibromata were found on the arms and thighs in association with many pigmented areas.

At operation.—Sir Percy Sargent performed an intracapsular removal of a walnut-sized left acoustic neurofibroma. Sixteen months later the patient's condition was substantially unchanged (apart from the absence of papillœdema) but it is not known what happened to him subsequently.

(*b*) H. H., male, aged 25. Admitted to the National Hospital in 1932 under Sir Gordon Holmes, complaining of an unsteady gait for four years, deafness and giddiness for eight months, and deteriorating vision with headaches and vomiting for six months.

Previous history.—15 months prior to his admission to the National Hospital, neurofibromata had been removed from the left phrenic and right ulnar nerves.

Family history.—The patient recalled that his mother had had numerous painful lumps on several nerves; 3 or 4 had been removed although at least 12 had been left untouched.

On examination.—Marked bilateral papillœdema, sensory impairment over the first and second divisions of the left trigeminal nerve with an absent left corneal response, slight left peripheral facial weakness with spasm, a deaf left ear (with reduced hearing in the other ear), slight left palatal weakness, slurring dysarthria, nystagmus and some weakness of the right arm and leg with a right extensor plantar response were found. The patient died shortly after operation and at post-mortem a large neurofibroma was found on the left acoustic nerve. In addition other neurofibromata were disclosed on the left brachial plexus, the third left lumbar posterior root, and on the dorsal surface of the first thoracic segment of the cord.

(*c*) F. L., female, aged 35. Admitted to the National Hospital in 1932 under Dr. Stewart, complaining of giddiness, tinnitus and deafness for two and a half years, headaches, right sided facial pain and clumsiness of the right limbs for one and a half years.

On examination.—No papillœdema was found but there was marked sensory and motor involvement of the right trigeminal nerve, slight right peripheral facial weakness, deafness of the right ear with reduced caloric responses, nystagmus and mild cerebellar ataxia of the right arm and leg. In addition she showed peripheral nerve lesions involving the right hand and the left common peroneal nerve, on

which a swelling was palpable; numerous pigmented patches were also visible on the trunk.

At operation two years later (she had refused operation previously) Sir Geoffrey Jefferson performed an intracapsular removal of a large cystic acoustic neurofibroma. The operation had to be repeated nine years later, and the patient died subsequently. No post-mortem was performed.

Whilst it is naturally difficult to compare 3 with 154 patients, it is evident that in general these 3 patients differed in no marked way from the others in our series with unilateral acoustic neurofibromata. One might note that their average age at the onset of symptoms was 24 years, and at the time of admission to hospital 36 years; both being substantially lower figures than those obtaining in the series as a whole. It might also be worthy of comment that in 2 of the 3 patients the tumour was clearly of very slow growth. However, such comparisons can be of little value for obvious reasons.

Bilateral acoustic tumours.—As has already been mentioned, 6 of the 7 patients with bilateral tumours included in this series showed indisputable evidence of generalized neurofibromatosis, 4 coming to post-mortem examination. In 5 of the 6 this complication was of a mixed central and peripheral type, but in only 1 of the 6 was there a clear family history of a similar disorder. This patient had a brother who had been diagnosed as having von Recklinghausen's disease and who had been operated on elsewhere for multiple intracranial tumours.

Cushing (1917) stated in connexion with unilateral acoustic tumours that "no familial examples have even been recorded, nor any recognizable tendency in the direction of parental generalized neurofibromatosis." Our series provides no exception to the former part of Cushing's statement, and we are not aware of any mention of familial unilateral tumours in the literature. However case H. H. detailed above is of interest in that his mother probably had neurofibromatosis. Revilla (1947) also records 3 instances in which patients with unilateral acoustic tumours showed evidence of neurofibromatosis. He too noted that their average age at onset of symptoms and on admission was considerably lower than for the group as a whole, as well as the fact that their average duration of symptoms was some ten years, or twice as long as for cases without this complication.

The familial inheritance of bilateral acoustic neurofibromata is of some interest, and several outstanding examples have been recorded. Gardner and Frazier in 1930 detailed the history of a remarkable family in which 38 of 217 members over five generations developed bilateral deafness which was apparently transmitted as a Mendelian dominant; 15 of the 38 subsequently became blind. They were able to examine 7 members with deafness and 4 with blindness; 5 of the former showed

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absent vestibular responses in addition to deafness, and all 4 of the latter showed papillœdema with consecutive optic atrophy. Although they were unable to obtain confirmatory evidence by operation or post-mortem, they justifiably concluded that the affected members of this family had familial bilateral acoustic neurofibromata. Yet a further point of interest was that practically no associated evidence of von Recklinghausen's disease was found in the members examined. Minski (1932) reported 3 members of one family belonging to the same generation; 2 had bilateral acoustic tumours (1 with generalized neurofibromatosis in addition) and the third showed neurofibromatosis of the cord only. Again Revilla (1947) noted that 2 patients (who were sisters) in his series of bilateral cases came from a family which gave a history on the maternal side which was strongly suggestive of familial acoustic tumours. Thus all of the 35 individuals involved developed bilateral deafness when young, and all died within approximately five years of the onset of symptoms. 3 in addition apparently showed evidence of generalized neurofibromatosis. We have no such instances of familial bilateral acoustic neurofibromata to add to the literature. It is clear, however, that not only is the condition occasionally hereditary, but in addition it may be passed down from generation to generation with no or very few accompanying features of von Recklinghausen's disease.

TABLE XX.—THE INCIDENCE OF PAPILLŒDEMA IN RELATION TO THE YEAR OF ADMISSION TO HOSPITAL

Year of admission	*No. of patients*	*Papillœdema*
1921–30	29	24 (83%)
1931–35	28	24 (86%)
1936–40	30	24 (80%)
1941–45	23	16 (70%)
1946–48	47	31 (66%)
Total	157	119 (76%)

CONCLUSIONS

Although acoustic neurofibromata are pathologically innocent and often slow growing tumours, a disappointingly high proportion of patients show unequivocal evidence of a raised intracranial pressure by the time they are admitted to hospital. Thus 76 per cent of patients with unilateral tumours in this series showed papillœdema at this time and furthermore, as Table XX shows, little improvement in this state of affairs took place over the twenty-five years covered by this series. Whilst an enquiry into the causes of the admittedly high operative mortality of this tumour is beyond the scope of this paper, it is surely reasonable to suppose that if the diagnosis was commonly made at an earlier stage

the operative risks would be appreciably lowered, and the patient would be spared many disabling complications.

The early diagnosis of acoustic neurofibromata clearly hinges on an accurate evaluation of the initial symptoms which, it will be recalled, are those referable to the acoustic and trigeminal nerves followed by headaches and cerebellar ataxia. Furthermore as Table XIX shows, although acoustic symptoms were among the first to appear in 75 per cent of patients, a fair number complained of other symptoms at the onset. For this reason we believe that the chronological order of symptoms defined by Cushing (1917) is of little practical value in helping to establish an early diagnosis, and we feel that some authors have accorded it too much importance.

As is well known acoustic symptoms not infrequently escape notice altogether or are only mentioned by the patient in response to a direct enquiry. It is perhaps not too much to say, furthermore, that mild unilateral deafness with or without tinnitus is usually regarded by both the patient and his doctor as an unimportant complaint in adults, whilst occasional episodes of "giddiness" or vertigo do not cause additional concern unless they are disabling. It will be recalled that though these symptoms were commonly encountered in our series they were not usually conspicuous. At this stage then, if the patient seeks medical advice at all, his symptoms as often as not will be ascribed to some common and benign aural condition and be awarded little attention. Later on, the addition of headaches, which are rarely severe initially, is unlikely to lead to a prompt reconsideration of the previous diagnosis, whilst early unsteadiness of gait of cerebellar origin is often attributed to aural factors. In this way some two to three years on an average may elapse before the suspicion is entertained that a progressive and serious condition is responsible for these symptoms. When one considers furthermore how this tumour as a cause of deafness, tinnitus and vertigo is completely overshadowed by more common aural conditions, it is only too easy to understand how its bearers are rarely seen by neurologists and neurosurgeons before the growth has reached a relatively advanced stage.

We have already ventured the opinion that signs of involvement of the cerebellar system or evidence of trigeminal sensory loss—in particular impairment of the corneal reflex—can, in association with deafness, be regarded as having cardinal diagnostic importance. These signs have in addition the merit of being simple to elicit and mostly objective in nature. It is surely not unreasonable therefore to urge those who are most likely to encounter early cases to look for nystagmus, observe gait and stance closely, and to examine the corneal reflexes carefully as a routine measure in all appropriate instances, even though they lack the time to perform a full neurological examination. The use of special

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investigations which can readily be applied in certain clinics deserves more notice: it is known how valuable radiological studies of the temporal bone can be in experienced hands, whilst the recent contributions made by otologists using special tests of cochlear and vestibular function have considerably increased the possibilities of early diagnosis.

In short, though the initial symptoms of an acoustic neurofibroma are not often of such a nature as to lead to prompt diagnosis, if more attention were paid to the early signs stressed above, and if special radiological and otological procedures were used more frequently, there is every chance that the neurosurgeon would be able to achieve far better results than are currently obtained in dealing with this important intracranial tumour.

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THE FAMILIAL INCIDENCE OF DISSEMINATED SCLEROSIS AND ITS SIGNIFICANCE

BY

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In the past a diagnosis of disseminated sclerosis in more than one member of a family has been accepted with considerable reserve, unless verified pathologically. This has been due to the difficulty in distinguishing the progressive form of disseminated sclerosis from familial spastic ataxia and paraplegia. The primary purpose of this paper is to assess the familial incidence of disseminated sclerosis in an unselected series of cases and briefly to discuss its significance.

Historical Note

The earliest authoritative reference to the familial incidence of disseminated sclerosis appears to have been made by Gowers, who in 1893 wrote: "Direct heredity, or the affection of two brothers or sisters, has been noted in a few instances, but is quite exceptional." Eichhorst's (1896) instance of the disease in a mother and her son has not received general acceptance on the grounds that the onset of symptoms in the son occurred at the age of 8 or earlier, and that at autopsy no sclerotic patches were found in the brain-stem of either case despite the presence of ocular paralysis. In France, at the beginning of the present century, a familial form of disseminated sclerosis, distinct from familial spastic paraplegia, was recognized (Cestan and Guillain, 1900). In this country Reynolds (1904) gave an account of the disease in a sister and two brothers, and also in two sisters. However, the comparative rarity of published cases at that time seemed to confirm Gowers' opinion. Risien Russell (1911), in an excellent account of the disease, wrote: "It is only exceptional that any direct heredity has been traced or that more than one member of the same family has been affected in the way obtained in Reynolds' cases." Oppenheim (1911), in his well-known textbook, made no reference to heredity as a factor in the ætiology of disseminated sclerosis. Brain

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(1930) in a critical review wrote: "Some reported instances of the familial occurrence of disseminated sclerosis are now recognized to have been examples of other conditions. . . . In other cases the diagnosis in the absence of autopsy must remain doubtful. . . . In striking contrast to diseases attributable to an inherited germinal defect, multiple cases of disseminated sclerosis in one family are extremely rare compared with sporadic cases, and its occurrence in more than two members of a family, and in two successive generations, is almost unknown. These facts suggest that inherited predisposition plays no part in the ætiology of the disease, and that the occasional occurrence of multiple cases in a family is due either to chance, exposure to a common environment, or mutual infection." In the last edition of his book (1947) some modification of this view may be inferred from his statement that the proportion of patients with disseminated sclerosis who have a near relative similarly affected lies between 5 and 10 per cent. In a personal communication he states that a recent survey of a further series of 93 patients has confirmed this estimate. However, other writers of recent textbooks have maintained a conservative attitude towards this question. Kinnier Wilson (1940) prefaced his remarks on the hereditary and familial incidence of the disease by pointing out that "alleged examples of the familial form, and others resembling the disease, but with pronounced heredo-familial incidence, must not seldom be relegated to another category." He referred to two families among his own patients, in both of which the disease occurred in two sisters—a remarkably small number considering the wide experience of the writer. Wechsler (1947) states: "Heredity plays no role although isolated cases have been reported in mothers and children."

In recent years the only noteworthy contribution to this subject was made by Curtius (1933). He made inquiries amongst 3,129 relatives of 106 cases of disseminated sclerosis observed in Bonn and Heidelberg. He found 8 instances in which the disease had affected more than one member of the family. Later two more positive family histories were discovered in the same series (Curtius and Speer, 1937). 4 of the cases occurred in sibs, one case in a parent, and the remainder in more distant relatives. Curtius also investigated 640 relatives of 56 patients with fractures. No case of disseminated sclerosis was found in this group. On the basis of these figures, and of the morbidity rate of disseminated sclerosis as determined in the Swiss Survey (Bing, 1932), Curtius concluded that the incidence of secondary cases of disseminated sclerosis in the families of his patients was markedly raised as compared with a control population. He was also impressed by the incidence of such anomalies as inner ear deafness, tremor, stammering and various mental disorders amongst relatives. These two concepts are embodied in his later conclusions (Curtius and Speer, 1937): "Das eine ist nach unseren Zahlen jedenfalls sicher, dass

eine *spezifische,* nicht eine unspezifische Disposition zur MS–Entstehung vererbt wird, die allerdings in irgendeiner Weise mit einer allgemeineren neuropathischen Erbkonstitution in Zusammenhang steht. Die letztere ist unspezifisch and findet sich bei den verschiedensten Nervenleiden." ("From our figures it is clear that a *specific,* not an unspecific disposition to disseminated sclerosis is inherited, which, however, is connected somehow with a more general neuropathic constitution. The latter is unspecific and occurs in various nervous diseases.") McAlpine (1946) in reporting 8 examples in a series of 142 cases stated "that the familial incidence of the disease is significant and an inherited constitutional factor might render an individual more susceptible to it." Mackay (1950) in surveying the literature of familial cases of disseminated sclerosis excluded those unaccompanied by clinical descriptions. This accounts for his low figure of 55 families with 177 affected persons. To this number he has added 5 more families. He concludes that disseminated sclerosis shows a familial incidence more frequent than mere chance would determine, and that this is due to a familial constitutional vulnerability to the disease.

A list of published cases affords no guide to the true familial incidence of disseminated sclerosis. It is certain that many cases go unrecorded. As Symonds (1949) has recently stated: ". . . every neurologist has his own collection of these." Our own experience would suggest that the reported incidence of familial examples of the disease will vary according to the thoroughness with which the inquiry is conducted, and the number of relatives covered by it. A special interest in this subject will sometimes result in the reporting of a number of familial cases from the same locality. Obständer (1926) recorded 4 instances, while Redlich (1928) contributed 3 more from the same hospital in Vienna (Maria-Theresien Schlössel). Simon (1927) cited 6 examples from Heidelberg, while Curtius (1933) and Curtius and Speer (1937) added 4 more from the same city.

An attempt has been made to arrange the familial cases of disseminated sclerosis reported in the literature into three groups: Group I—details of each affected member of the family given in the original paper; Group II—details of only one case given; Group III—no description of cases given. References to these cases are included in Appendix II. In each of these groups the diagnosis has been accepted, either from the clinical or pathological findings, or on the status of the reporter. For a variety of reasons a number of cases have been rejected. From Appendix II it will be seen that at least 184 instances of disseminated sclerosis in more than one member of a family have been reported.

The following table (Table I) shows the reported familial incidence of disseminated sclerosis in various series.

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TABLE I.—FAMILIAL INCIDENCE OF DISSEMINATED SCLEROSIS IN PUBLISHED SERIES

Author	*Familial cases in series*
Klausner (1901)	2/126
Berger (1905)	3/206
Bramwell (1917)	2/200
Schultze (1919)	1/about 200
Wechsler (1922)	1/197
Obständer (1926)	5/270
Allison (1931)	1/65
Marburg (1932)	3/152
Bing (1932)	13/891
Adie (1932)	1/118
Curtius (1933) Curtius and Speer (1937)	10/106
Barré (1936)	0/300
Curschmann (1938)	2/150
Schaltenbrand (1939)	6/400
Sällström (1942)	17/1015
McAlpine (1946)	8/142 (patients included in present series)
Millar (1949)	3/91
Steiner (1949)	6/160

PRESENT MATERIAL

The greater part of the material reported in this paper is taken from two groups of cases. Group I (Families A–H, Appendix I), which consists of 142 patients, was reported by one of us (D. McA.) in 1946, but was not at that time subjected to a detailed familial study. Group II (Families J–U, Appendix I) consists of 168 patients seen by us for the first time between April 1, 1948, and September 30, 1949. In addition 13 families which have been seen at various times are included for the purpose of the genetical analysis. Because of their clinical interest certain of these (Families V, W, and X) are referred to in the main text; only the material from Groups I and II is used in assessing the familial incidence of the disease.

METHOD OF INQUIRY

All cases in Groups I and II were subjected to an oral questionnaire; in Group I inquiry was limited to the health of parents and sibs, whereas in Group II it was extended to cover grandparents, parents, aunts and uncles, sibs, cousins, children, nephews and nieces. Patients were questioned about the health of each relative; if from this inquiry a neurological disease seemed probable, the affected relatives were approached and asked to give the name of their general practitioner, of any neurologist they might have seen, and of any hospital they had attended. With this information medical records were obtained and the diagnosis established. In some instances affected relatives were visited, a full history taken and an examination made.

It was more difficult to obtain exact information about deceased relatives. Here again we obtained the name of the general practitioner, neurologist or hospital the patient had attended or in which he or she had died. A few cases had to be excluded for lack of positive information. For example, the following family history is highly suggestive of a diagnosis of disseminated sclerosis, but has been rejected because there are no medical records or medical opinions available on the secondary cases.

Family Y.—Two brothers and their half-sister.

W. C., male, born 1908. Aged 32 blurring of vision in the right eye, lasting five weeks. Patient was seen at Moorfields Hospital, where a diagnosis of retrobulbar neuritis was made; nystagmus was also noted. The Lange curve was 0122222100, but the C.S.F. was otherwise normal. Aged 35 he had a left facial weakness followed by right facial weakness, with recovery. Aged 39 he noticed urgency of micturition. Aged 40 he had dragging of the right leg and clumsiness of both hands with remission. He was seen at the Middlesex Hospital on 30.3.49, aged 41, when examination (N. D. C.) showed pallor of the optic discs, left more than right, an increased jaw-jerk; increased reflexes in the right arm with an intention tremor; absent abdominal reflexes; the lower limb reflexes were increased and the plantar responses were extensor; vibration sense was absent in the legs.

The patient gave the following history of his brother and half-sister.

C. C., male, born 1910. Aged 26 sudden onset of mistiness of vision. He later developed leg weakness and is now helpless and incontinent.

I. L., female, born 1899, died about 1938. Onset of paralysis aged 28, later became helpless with difficulty in swallowing and urinary incontinence.

With one exception, only those cases have been included in which adequate medical records of the secondary cases were obtained. These cases are reported in Appendix I. In the case accepted without obtaining medical records (Family H), the diagnosis of disseminated sclerosis was made at three London hospitals, and the history of the case obtained from an intelligent relative was considered so typical of the disease as to warrant its inclusion.

Results

In Group I, consisting of 142 cases, a positive family history was proved in 8 patients. The inquiry, as has been stated, was limited to the history of parents and sibs. In Group II, where the inquiry was widened to include additional relatives, 168 cases showed a positive family history in 12 instances, an incidence of 7 per cent. Therefore Groups I and II, consisting of 310 cases, give a familial incidence of 6·5 per cent.

In Group I the secondary cases occurred in the parents on two occasions and in the sibs on six occasions. Further inquiry revealed in addition to a sib an affected cousin of one of these patients. In Group II a parent was affected in 1 family, sibs in 6, a first cousin in 3, a maternal aunt in 1, a fraternal nephew in 1, and a paternal uncle in addition to a sib in 1 case. Thus the secondary cases occurred amongst

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sibs in 12 families, amongst parents in 3 families, and amongst more distant relatives in the remaining families.

It was obviously impossible to discover the total number of relatives in all families in order to calculate the actual incidence of the disease amongst them, but in Group II we noted the total number of sibs of our 168 patients. These patients had 538 living sibs, amongst whom were 5 living cases of disseminated sclerosis (1 of the 6 referred to above was dead). This figure gives an incidence of disseminated sclerosis amongst living sibs of approximately 1/108.

In our two groups (310 patients) there was a total of 620 parents, some of whom were dead. The average maternal age at the birth of our patients was 30, and the average age at which our patients were first interviewed was also 30. From life tables it is possible to calculate that about one-quarter of the population aged 30 will die before reaching the age of 60. At the time our patients were interviewed, approximately three-quarters of their parents would therefore have been living, amongst whom were 3 affected with the disease. The incidence of disseminated sclerosis amongst the living parents of our cases was therefore 3 in approximately 465, or 1/155.

To appreciate the significance of the incidence of the disease amongst the sibs and parents of patients with disseminated sclerosis it is necessary to compare it with the morbidity rate in the general population. The morbidity rate in the population of England and Wales can be calculated from the following formula:

$$\frac{\text{Average number of deaths per year from disseminated sclerosis (1937–46)} \times \text{Average duration of disease in years}}{\text{Population of England and Wales (1931)}}$$

The average number of deaths per year from disseminated sclerosis, and the population of England and Wales, can be obtained from the Registrar General's Annual and Decennial reports. Greater difficulty is experienced in obtaining an estimate of the average duration of the disease. Within any series of cases, estimates based on average duration of life of those patients dying with the disease are fallacious, as they do not take into account those who are still living. The average duration of the disease reported in various series is given in Table II. The average duration in all series combined is 12·15 years.

In Müller's (1949) survey of disseminated sclerosis, his total material consisted of 793 cases registered at various hospitals in Stockholm and Uppsala between 1920 and 1945; of these 171 died from disseminated sclerosis and other causes. He used part of this material, namely 127 cases, in studying the risk of death for each five-year period up to twenty years from the onset of the disease. From these figures he calculated

TABLE II.—AVERAGE DURATION OF DISEASE IN DEAD PATIENTS

Author	*No. of dead patients*	*Av. duration in years of disease*
Bramwell (1917)	106	12·1
Brain (1936)	11	12·5
Drobnes (1937)	46	10
Sällström (1942)	285	9·2
Reinhold (1950) Institutional cases	216	17·7
National Hospital	56	7·6
Middlesex Hospital 1930–49 Males	15	11·8
Females	22	12·1
Total	757	12·15

that 38 out of every 100 patients in his series would be dead at the end of twenty years, with an average duration of life in these patients of 10·4 years. He calculated that if the remaining 62 in each 100 died immediately the average duration of life in all patients would be 16·4 years, whereas with a normal expectation of life the average duration would be 33·8 years from the onset of the disease. He estimated that the correct figure for the duration of the disease must lie between sixteen and thirty-four years.

Allison (1950) reviewed after twenty years a series of 40 unselected patients with disseminated sclerosis. The average duration of the disease among the 28 patients who had died was approximately twenty years; the inclusion of the 12 survivors in the calculation of the average duration of the disease indicated that for the whole series this would be somewhat greater than twenty-two years.

We have taken an arbitrary figure of eighteen years as representing the average duration of the disease in this country. Allison's figures and a preliminary survey of our own material of over 500 cases would suggest that this figure may prove to be an underestimate. The incidence of disseminated sclerosis in the general population of England and Wales is then estimated to be 1 in $\frac{867 \times 18}{39{,}988{,}000}$ or 1/2564. Since disseminated sclerosis rarely commences below the age of 15, the expected incidence of the disease in the population above this age is calculated as 1/2000. This figure is of the same order as that found by one of us (R. T. C. P.) in a survey made in 1949 of an area of 260 square miles around Stamford, Lincs., where 18 cases of disseminated sclerosis were found in a population of 41,000, an incidence of 1/2280. This is a lower figure than previously recorded, e.g. 1/8600 for North Wales (Allison, 1931), and 1/5000 for Cornwall, Berks, Bucks and Suffolk (Campbell *et al.*, 1950).

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The observed and expected incidence of disseminated sclerosis in the living parents and sibs of our patients is shown in Tables III and IV. The observed incidence in each case is significantly higher than the expected incidence, the risk of contracting the disease being approximately 18 times greater in the sibs of affected patients and 13 times greater in the parents of affected patients than in the general population. The former figure compares closely with that of 20 times greater arrived at by Curtius (1933), although his method of selection of a control population is open to criticism.

TABLE III.—OBSERVED AND EXPECTED INCIDENCE OF DISSEMINATED SCLEROSIS IN SIBS OF 168 PATIENTS

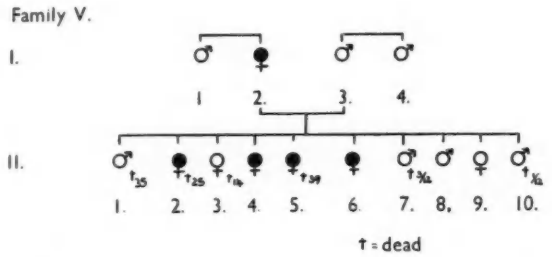
	No. of living sibs	*No. of affected living sibs*	
No. of patients	*above age of* 15	*Observed*	*Expected* (538/2000)
168	538	5	0·27 ± 0·52

TABLE IV.—OBSERVED AND EXPECTED INCIDENCE OF DISSEMINATED SCLEROSIS IN PARENTS OF 310 PATIENTS

		No. of affected living parents	
No. of patients	*No. of living parents*	*Observed*	*Expected* (465/2000)
310	465	3	0·23 ± 0·48

PEDIGREES OF SPECIAL INTEREST

Two families that we have studied are especially noteworthy because of their high incidence of the disease. These families will be described in detail.



It will be seen from the above diagram that the mother and four out of five daughters who survived to adult life became affected with the disease.

Case I.2.—A. E. H., mother, born 1880, died 1940. In 1928, at the age of 48, this patient was admitted to the National Hospital for Nervous Diseases, Queen Square, under the care of Dr. F. M. R. Walshe. Twenty-two years previously vision began to fail in the right eye; a diagnosis of iritis was made and an iridectomy was performed in 1907. The left eye became similarly affected in 1908. The right eye was excised in 1909. About 1916, at the age of 36, weakness of the right leg was noticed, which progressed. In 1925, aged 45, she developed weakness of the right arm. The same year she was admitted to the Maida Vale Hospital for

Nervous Diseases, when she had retention of urine and subsequently precipitancy and frequency of micturition. The case record from this hospital is not available. During the years 1925–28 her paresis had gradually progressed and she had a tendency to sway to the right when walking. Examination at the National Hospital (1928) revealed a coarse nystagmus on fixation to the left and a fine nystagmus to the right. There was limitation of upward movement of the eye. The remainder of the cranial nerves were normal. There was diminished power in all muscle groups of both arms, more on the right than on the left, with increase of tone and an ataxia of cerebellar type. Slight wasting of the muscles of the thenar and hypothenar eminences of the right hand was noted. The abdominal reflexes were absent. The right leg was spastic in extension; there was bilateral ankle clonus with extensor plantar responses. Sensation was normal in the arms, but there was loss of postural sensation and vibration sensation in both legs. A tendency to pes cavus was recorded. No lumbar puncture was performed. No further detailed records of her progress are available. She died at the age of 60 in a nursing home. Autopsy was not performed.

Case II.2.—D. H., born 1905, died 1930. At the age of 21 she complained of weakness and stiffness of the right leg, which dragged on walking. Six months later she noted tremor of the left hand on sewing and some speech difficulty. She had double vision on lateral deviation of the eyes. Early in 1928, aged 23, she was admitted to the West End Hospital for Nervous Diseases under the care of Dr. L. R. Yealland. The findings were similar to those recorded below. The cerebrospinal fluid contained 15 lymphocytes per c.mm., and 30 mg. per cent of protein. The W.R. was negative, and the Lange colloidal gold curve 5554210000. In June 1928 she was admitted to the National Hospital for Nervous Diseases, Queen Square, under the care of Dr. F. M. R. Walshe. Examination then showed dysarthria, bilateral ptosis, vertical and lateral nystagmus and occasional titubation. Otherwise the cranial nerves were normal. There was a slight spastic weakness of both arms and an intention tremor of the left arm. There was diminution of power in the right leg with some contracture of the right tendo Achillis. Tone was increased in both legs and there was a cerebellar ataxia of the right leg. There were no abnormal sensory signs. Tendon reflexes throughout the body were greatly increased and both plantar responses were extensor. The abdominal reflexes were feebly present. There was a slight upper dorsal scoliosis, but no other skeletal deformity. The cerebrospinal fluid then contained 3 lymphocytes per c.mm., 15 mg. per cent protein, with a positive Pandy test, and a Lange curve of 1234320000. The patient made no improvement in hospital and continued to deteriorate. She was admitted to Napsbury Mental Hospital 14.6.30, aged 25, as a certified patient owing to restlessness and inability to care for herself. She then showed generalized gross motor weakness but no detailed record of her physical state is available. She died six months after admission. At post-mortem the brain and spinal cord were examined and a diagnosis of disseminated sclerosis was made; no record of a histological examination can be obtained.

Case II.4.—L. H., female, born 1909. At the age of 16 she had a right-sided facial palsy lasting for three weeks. At the age of 19 she was seen at the National Hospital, Queen Square, by Dr. F. M. R. Walshe in connexion with the illness of her mother, Case I.2, and her sister, Case II.2. She was at that time symptom-free, but examination revealed the following abnormal signs in the central nervous system: nystagmus to right and left, generalized increase in the reflexes, more marked on the right than on the left, but flexor plantar responses. On 3.3.42, at the age of 33, she was admitted to the Middlesex Hospital under the care of Dr. P. Sandifer. She stated that in 1929 at the age of 20 she began to drag her feet on walking. At the age of 26 she had an attack of herpes in the distribution of the third branch of the trigeminal nerve, and following this her walking had

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steadily deteriorated so that by the age of 28 she had to use a stick. At the age of 30 she had an attack of double vision, and this recurred intermittently. Examination showed marked temporal pallor of both discs, horizontal and vertical nystagmus, but otherwise the cranial nerves were normal. Power was slightly diminished in the fingers of the right hand while the reflexes were increased in both arms. Joint sensation was impaired in the fingers of both hands. The lower limbs were spastic, more so on the right side, the plantar responses were extensor with bilateral ankle clonus. Postural sensation and vibration sensation were impaired in the right leg. There was a tendency to talipes equino-varus deformity of the right foot. Following her discharge her condition steadily deteriorated, and she was ultimately admitted to the Putney Home for Incurables. In 1949, at the age of 40, she temporarily lost the use of both hands completely for four days. The patient was visited by one of us (R. T. C. P.) on 7.10.49, when examination revealed pallor of both optic discs, vertical and lateral nystagmus, weakness of both arms with bilateral intention tremor. The arm reflexes were then absent. There was marked impairment of postural sensation in both hands, especially the right. The lower limbs were paraplegic in flexion. There is no record that this patient ever had an examination of the cerebrospinal fluid.

Case II.5.—V. R., female, born 1910, died 1949. The history of this patient has only been obtained late in her illness and is therefore lacking in detail. She commenced to drag her feet in 1933 at the age of 23, and following this developed a progressive paraplegia, so that by 1940 she was unable to walk. In 1942, aged 32, she had double vision and slurred speech. In 1943 she was admitted to Enfield House (later Chase Farm Hospital). She was completely bedridden from 1944 and was incontinent of urine and fæces. One of us (N. D. C.) was allowed to visit her by permission of Dr. Allan Birch, Medical Superintendent of Chase Farm Hospital. Examination (4.1.49, aged 39) revealed intense euphoria and a degree of dysarthria so marked as to make her speech incomprehensible. She had marked nystagmus on central fixation and an ataxic nystagmus on fixation to left and right. Both right and left internal recti were weak. Both optic discs were uniformly pale. Palatal movements were impaired, and tongue movements, though full, were slowly performed. There was a spastic paresis and generalized wasting of both arms. The arm reflexes were absent, and there was intense cerebellar ataxia. Sensation could not be adequately tested. The legs were in complete paraplegia in flexion and were markedly wasted. She died one month after this examination from bilateral pyelonephritis, and through the courtesy of Dr. Allan Birch we were enabled to examine the brain and spinal cord. Macroscopically the specimen showed widespread plaques throughout the brain and spinal cord, being particularly plentiful in the periventricular regions. Histological examination revealed the typical changes of disseminated sclerosis (fig. 1).

Case II.6.—V. G., female, born 1913. This case has been extensively studied at this hospital from 1944 onwards, when she was seen by Dr. P. Sandifer and subsequently admitted. In 1936, aged 23, she lost the use of her right arm for four days. In November 1938, aged 25, both legs became paralysed for one month: recovery was complete. In February 1944, three months after the birth of a child, she noticed blurring of vision in the left eye and weakness of the right arm and leg. In April 1944, aged 31, she was admitted to Mount Vernon Hospital under the care of Dr. P. Sandifer. Physical examination showed pallor of the temporal half of the left disc; and fine nystagmus to the left. The arms were normal apart from an intention tremor on both sides. There was an increase in the reflexes of the right leg, both plantar responses were extensor, and there was cerebellar ataxia in both legs but no sensory loss. The cerebrospinal fluid at that time was normal except for the presence of 22 lymphocytes per c.mm.; a Lange colloidal gold test was not performed. After her discharge from hospital she

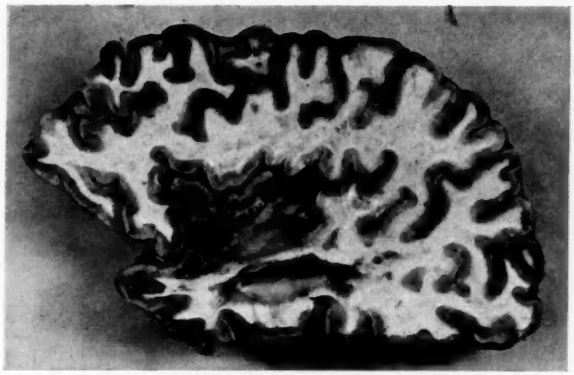

FIG. 1(*a*)

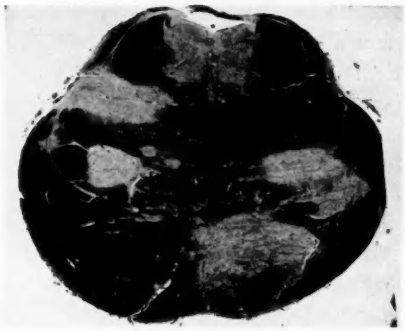

FIG. 1(*b*)

FIG. 1 (*Family V. Case II.5*).—(*a*) Periventricular demyelination around temporal horn. (*b*) Discrete plaques of demyelination in pons.

remained well until November 1944 when she developed attacks of vomiting, followed by double vision and numbness in both arms. The numbness later spread to involve the trunk and legs, and was associated with a return of weakness in the legs. She was readmitted to hospital in January 1945. She was now dysarthric. The jaw-jerk and arm reflexes were increased and the lower limbs were spastic with bilateral extensor plantar responses. Position sense and vibration sense were disturbed in all four limbs. There was retention of urine with overflow incontinence. After a fortnight she began to improve, and by May she was walking unsupported, although she had a typical spastic gait. The patient was not seen again until 13.7.48, aged 35. She then stated that following her discharge from hospital she had lost the sight of the right eye for two months, but that after this episode there had been a gradual improvement so that she was able to do her own housework and shopping. Examination (N. D. C.) showed pallor of the temporal halves of both discs, nystagmus on central fixation and on lateral and vertical gaze, and an increased jaw-jerk. The arms were normal apart from increased reflexes and a mild degree of interior tremor. She had a moderate spastic paraplegia, more marked on the right than on the left, with increased reflexes and extensor plantar responses.

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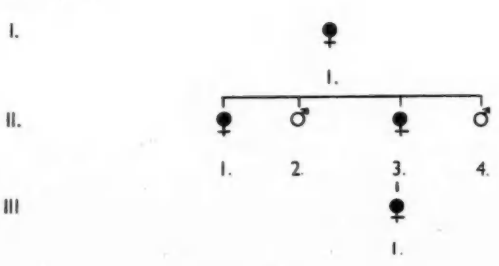
There was a minimal loss of postural sensation in the right leg and a complete loss in the left leg, with resultant ataxia. Vibration sensation was diminished in both legs. No sensory level to vibration could be detected. Since that time this patient has been seen at six-monthly intervals. In January 1949 she developed double vision, numbness of the right side of the face, clumsiness of the right arm and further weakness of the right leg. This relapse lasted only ten days and when seen after this attack her physical state was the same as when previously examined. However, in February she had an attack of weakness in both legs, more marked on the right than on the left. When examined after this attack there was a more marked residual paresis of the right leg amounting to about 60 per cent loss of power. The patient was last seen in September 1949, when she reported no further episodes, and physical examination revealed no change except for a little improvement in the power of the right leg.

The mother and eldest daughter (Cases I.2, II.2) were patients in the National Hospital at the same time in 1928. The third daughter (Case II.4) also attended there for examination although she was at that time free from symptoms. The possibility of disseminated sclerosis was discussed but the consensus of opinion favoured a diagnosis of a familial neuronic degeneration allied to Freidreich's ataxia. When the histories of each of these patients are considered, it is clear that in Cases I.2, II.2 and II.5 the clinical picture was one of a progressive ataxic paraplegia without any external ophthalmoplegia. The clinical picture was therefore compatible with a familial form of spastic ataxia, apart from the abnormal cerebrospinal fluid in Case II.2. However, post-mortem examination of Cases II.2 and II.5 definitely established the diagnosis of disseminated sclerosis. In Cases II.4 and II.6 a diagnosis of disseminated sclerosis is amply justified on clinical grounds. In both cases there is a history of remissions and relapses and of disturbances of postural sense at some time in the course of each illness. In addition Case II.6 gave a history of retrobulbar neuritis and her cerebrospinal fluid on one occasion contained 22 lymphocytes per c.mm. Therefore, since in this family of five affected persons the diagnosis of disseminated sclerosis was made pathologically in two instances and in two other members was reasonably certain on clinical grounds alone, it may be inferred that the mother of the family was also a victim of the same disease.

Family W.



Case I.1.—M. S., female, born 1873, died 1933. At the age of about 35 years the patient noticed weakness of the legs and tremor of the hands. A diagnosis of disseminated sclerosis was made at that time. The disease pursued a fairly favourable course with mild relapses and remissions, but on the whole slight deterioration, until the age of 60. She then developed nocturnal bladder incontinence and increasing weakness. It was noticed by her relatives that her speech and gait were more affected than usual. Following a fall after the onset of this relapse she was unable to walk at all because of severe weakness in the left leg. There was rapid mental deterioration at this time. When examined on 23.1.33, aged 60 (D. McA.), she showed considerable impairment of memory and marked dysarthria. There was pallor of the temporal halves of both optic discs and lateral nystagmus. The remaining cranial nerves were normal. Power in the arms was greatly diminished and the reflexes were exaggerated. Both arms showed marked cerebellar ataxia. She had a severe degree of spastic paraplegia with exaggerated reflexes and bilateral extensor plantar responses. There was diminution of all forms of sensation in both legs, left more than right, with a level at D2; however, sensory examination in view of her state of mind was not considered reliable. The patient died a few months later.

Case II.1.—M. C., female, born 1896, died 1931. This patient was seen in March 1928 by one of us (D. McA.) when she gave a history of an attack of double vision at the age of 20. Following this she was well for five years, when she developed weakness of the legs. The onset of this leg weakness was accompanied by a persistent cold feeling around the waist. In the winter of 1927, at the age of 31, she temporarily lost the vision of the right eye and about that time developed frequency and urgency of micturition. A diagnosis of disseminated sclerosis was made at that time, but no record of her physical state then is available. She had been seen previously by Dr. S. A. Kinnier Wilson and by Dr. Gordon Holmes, both of whom had made a diagnosis of disseminated sclerosis. In 1931, at the age of 35, she had a severe exacerbation and died.

Case II.3.—M. S. B., female born 1898. This patient was first seen by one of us (D. McA.) on 30.8.26. In 1923 at the age of 25 she noticed heaviness of the legs associated with pins and needles in all four limbs. At the age of 27 she developed difficulty in starting micturition. Examination on 30.8.26, aged 28, showed pallor of the temporal halves of both discs but no nystagmus or other cranial nerve abnormality. The arms were normal except for an ataxia on the left of cerebellar type and increased reflexes. The abdominal reflexes were absent. There was a mild paraplegia with increased reflexes and extensor plantar responses, and cerebellar ataxia of slight degree in both legs; sensation was normal. The patient was seen at frequent intervals between 1926 and 1932. During this period there was a gradual deterioration in her condition, but examination on 8.1.32 showed no new manifestations of the disease, only a more severe paraplegia. The patient was last examined on 12.11.36, aged 38, when she showed euphoria, pallor of the temporal halves of both discs, but no nystagmus. Power in the arms was normal; the reflexes were now increased, more on the right than on the left. There was a bilateral intention tremor. She had a moderately severe spastic paraplegia with loss of power about 60 per cent on the right and about 50 per cent on the left. There was ankle clonus. Vibration sense was diminished in both legs but postural sensation was normal. The patient is known to be alive and little more disabled than she was at this time.

Case III.1.—D. B., female, born 1921. We are indebted to Dr. C. C. Worster-Drought for allowing one of us (D. McA.) to interview this patient. In May 1937, at the age of 16, she developed slight numbness of the left foot which gradually spread up to the waist over a period of four weeks. The leg felt particularly

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abnormal in hot water at this time, though heat was appreciated. These symptoms disappeared spontaneously. In May 1943, aged 22, the numbness reappeared for three days and cleared up except for a persistent numbness in one toe. A month later she developed difficulty in picking her feet up on occasions when she was particularly tired. Between February and March 1944 the numbness again spread up the left leg and after five to ten minutes' walking her leg began to drag. At that time also there was occasional numbness in the left thumb and right upper lip. There was also mistiness of vision lasting for one hour only at this time. Since then her condition has remained almost stationary. The legs still drag after a short period of walking. There has also been frequency of micturition and on two occasions incontinence of urine. Examination on 17.5.49, aged 28, showed some euphoria, pallor of the whole of the right disc and temporal half of the left disc, horizontal nystagmus and an increased jaw-jerk. Power in the arms was normal but the reflexes were increased. There was an intention tremor of both arms, more marked on the left than on the right. Sensation in the arms was normal. She showed a mild spastic paraplegia with about 30 per cent loss of power on the left and about 20 per cent on the right. The tendon reflexes were increased in both legs, left more than right, and the plantar responses were extensor. There was marked cerebellar ataxia of both legs, and a typical spastic ataxic gait.

We have been unable to obtain records of examination of the cerebrospinal fluid of any members of this family. The family is reported in full because it is the only instance, either in our own series or in the literature, in which the disease has appeared by direct transmission in three generations. Marburg (1932) observed the disease in three generations, but in this instance the disease appeared in two sisters, a maternal aunt, and the maternal grandmother.

A Comparison of the Hereditary Degenerative Diseases and Disseminated Sclerosis

Friedreich's paper "Uber degenerative Atrophie der spinalen Hinterstränger" (1863), and that of Marie (1893) "Sur L'hérédo-ataxie cérébelleuse," led to the recognition of those degenerative disorders affecting the cerebellum and spinal cord which may be familial. They may be roughly classified as follows:

(1) Olivo-ponto-cerebellar atrophy (Dejerine and Thomas, 1900). Although the majority of cases conform to a cerebellar pattern, others show in addition pyramidal and extra-pyramidal signs (Greenfield, 1934; Titica and Van Bogaert, 1946). The late onset and progressive course of olivo-ponto-cerebellar atrophy and its variants usually enable a diagnosis to be made during life and confusion with familial examples of disseminated sclerosis is less likely than in the spino-cerebellar ataxias.

(2) The spino-cerebellar ataxias. This group includes Friedreich's ataxia and varieties of spastic ataxia, and paraplegia. Within this group considerable variations may occur, sometimes in a single pedigree. This fact may assume diagnostic importance, since the occurrence in a family of a typical case of Friedreich's ataxia, for example, may throw light on the

nature of a spinal cord disorder in other members of the same family. Since the classical case of Friedreich's ataxia is unmistakable, consideration will be limited to those forms of hereditary spinal ataxia which resemble disseminated sclerosis. It is clear that certain symptoms and signs are common to both groups of disorder, notably those concerned with cerebellar and pyramidal function such as dysarthria, tremor, unsteadiness of gait, and a spastic weakness of the lower limbs. Discussion will be limited to those points in the differential diagnosis which seem to be of major importance.

In the spino-cerebellar ataxias, symptoms usually declare themselves before the age of 20 years; occasionally they may not do so until the third or fourth decade, a later onset being more common when the disease appears to be transmitted by a dominant gene (Bell and Carmichael, 1939). The appearance of symptoms of disseminated sclerosis before the 20th year is limited to about 15 per cent of cases, the major incidence falling in the third and fourth decade. Of more importance is the age of onset in pairs of sibs. "One of the very striking facts of hereditary ataxia which quickly becomes apparent by visiting amongst afflicted families is the tendency of siblings to first show signs of the disease at the same period of life" (Bell and Carmichael, 1939). In disseminated sclerosis, on the other hand, there is a much smaller degree of correlation in the age of onset in pairs of sibs.

It is generally agreed that paræsthesiæ and impairment of sensation, more particularly of postural sense, are seldom met with in the hereditary forms of ataxia and paraplegia (excluding Friedreich's ataxia), whereas in disseminated sclerosis they form a distinctive feature. Failure of vision due to optic atrophy has long been recognized as a feature of certain families affected by ataxia or spastic paraplegia. In the 14 English families collected by Bell and Carmichael (1939) there was, however, no complaint of failing vision. In 7 out of 13 cases of spastic ataxia the discs were pale; in a further 4 cases the pallor was confined to the temporal half of the discs. When failure of vision does occur in the familial ataxias it tends to be progressive. These facts contrast with the frequency of a history of retrobulbar neuritis in disseminated sclerosis and the comparative rarity of a severe degree of permanent impairment of vision in this condition.

The differences in the courses pursued by these two disorders is usually striking. In the degenerative diseases under discussion the onset is usually so gradual that it may be difficult to determine the age at which it first declared itself. The course is one of slow progression, although in some cases there may be a period, varying in length, during which the signs remain stationary. This progressive course contrasts strikingly with the

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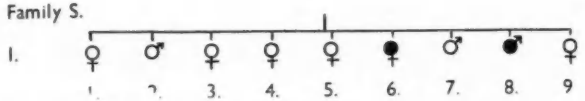
episodic nature of symptoms in the majority of cases of disseminated sclerosis. Nevertheless, within the last category there are cases in which a progressive paraplegia, particularly in the middle-aged, may closely resemble that seen in familial spastic paraplegia. This point will be discussed later.

Examination of the cerebrospinal fluid may be helpful in diagnosis, since in disseminated sclerosis there is often an increase in the protein content of the fluid and a positive Lange colloidal gold or benzoin curve; in the familial spinal ataxias the fluid is normal.

A comparison of the relative frequency in the population of familial cases of disseminated sclerosis on the one hand and of the familial forms of spastic ataxia and paraplegia on the other can only be made in general terms. Disseminated sclerosis would now appear to be one of the commonest organic diseases of the central nervous system in the United Kingdom. It follows from this premise and from the figures given in this paper that familial examples of disseminated sclerosis must no longer be considered exceptional. Bell and Carmichael (1939), using the records of the National Hospital, Queen Square, and the Maida Vale Hospital for Nervous Diseases, between the years 1926 and 1939 collected 13 families with 37 members affected by a spastic ataxia, and one family containing 3 males suffering from a pure spastic paraplegia. These figures include a great majority, but not all, of such cases seen at these hospitals in this fourteen-year period. It is therefore clear that the forms of familial degenerative disorder which may resemble disseminated sclerosis are rare in this country.

Some of these diagnostic points will not apply to cases of progressive paraplegia in one or more members of a family starting after the second decade. The following examples illustrate the difficulty in differentiating between disseminated sclerosis and the familial degenerative disorders of the spinal cord.



Case I.6.—H. H., female, born 1887, died 1949. Aged 43, onset of weakness of legs, especially right. The weakness was progressive, and no other symptoms had arisen when at the age of 53 she was admitted to the National Hospital, Queen Square, under the care of Dr. Gordon Holmes. Examination then showed normal fundi, no nystagmus, normal power in the arms but increased reflexes, absent abdominal reflexes, and a severe spastic paraplegia with knee and ankle clonus and bilateral extensor plantar responses. There was no sensory loss or cerebellar ataxia. The C.S.F. contained 50 mg. per cent protein but was otherwise normal. The patient continued to deteriorate, and when seen by one of us (D. McA.) on 22.3.49.

aged 62, she had developed weakness of the right arm in addition to further weakness of both legs. There was then absent vibration sensation in the legs. Subsequently her condition rapidly deteriorated, and when examined (R. T. C. P.) just before her death she showed additionally ataxic nystagmus with paresis of the right external rectus.

Case I.8.—R. D., male, born 1889. Aged 20, after a long march noticed dragging of the right foot. A year later unsteadiness of gait was noticed and persistent dragging of the right leg on exercise. By the age of 28 both legs were affected. A diagnosis of disseminated sclerosis was made by Sir Clifford Allbutt. There was slow progression, and at the age of 47, although still able to walk with two sticks, he was admitted to the British Home for Incurables at Streatham. He had occasional difficulty in starting micturition at that time. At no time did he complain of eye symptoms or arm symptoms, and there were never any paræsthesiæ. Examination by one of us (R. T. C. P.) on 30.9.49, when patient was aged 60, showed normal fundi and horizontal and vertical nystagmus. The arms were normal except for increased reflexes, the abdominal reflexes were absent, there was severe spastic paraplegia with ankle clonus and extensor plantar responses. There was no disturbance of vibration or position sense.

The progressive nature of the paraplegia and the absence of sensory changes in these 2 cases might have favoured a diagnosis of familial spastic

FIG. 2 (*Family S. Case I.6*).—Horizontal section of brain, showing a large plaque of disseminated sclerosis in right frontal region and others around the occipital horns.

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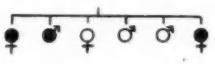
paraplegia although the different ages of onset are not typical of this condition. At the post-mortem examination on the first case typical lesions of disseminated sclerosis were found in the brain, brain-stem, and spinal cord (Dr. W. McMenemy, fig. 2). It is a reasonable assumption that her brother is suffering from the same disease.

Family X.

I.



1. 2. 3. 4 5. 6.

Case I.6.—E. S., female, born 1903. Aged 30, attack of pins and needles and numbness of the left arm lasting six weeks. Aged 32, similar attack. Aged 44, noticed dragging of the right foot and clumsiness of the left hand. Admitted to Middlesex Hospital 19.11.47, aged 44, when examination (D. McA.) showed normal fundi, no nystagmus, slight weakness of right arm with increased reflexes in both arms, but no sensory loss or ataxia. Abdominal reflexes were present. She had a moderately severe spastic weakness of the right leg, reflexes were increased in both legs and both plantar responses were extensor. Vibration sensation and postural sensation were normal. C.S.F. contained 4 cells per c.mm., 40 mg. per cent protein, and a Lange colloidal gold curve of 2344320000. When last seen 11.4.49 her condition was unchanged except for the reappearance of tingling and numbness in the left hand. Examination (N. D. C.) showed in addition to the previous findings horizontal nystagmus and slight impairment of vibration sensation in both legs.

Case I.1.—E. B., female, born 1889. Aged 38, noticed gradual onset of difficulty in walking, worse in the left leg than in the right. There was steady progression of weakness in the legs. At this time she had occasional attacks of vertigo lasting a few minutes. Aged 49, admitted to St. Bartholomew's Hospital under the care of Dr. D. Denny-Brown, who made a diagnosis of disseminated sclerosis. Examination showed no abnormality in the cranial nerves or arms, but a spastic paraplegia more marked on the right than on the left, with extensor plantar responses. There was no sensory loss. C.S.F. was entirely normal. There was only slight deterioration in her condition over the next ten years, with the arms remaining unaffected. Examination aged 60 (R. T. C. P.) showed pallor of the temporal half of the left disc, no nystagmus, increased reflexes in the arms which were otherwise normal, a severe spastic paraplegia with diminished vibration sensation at both ankles.

Case I.2.—H. T., male, born 1891. Age 40, temporary loss of the use of hands and feet, with subsequent weakness of the legs. Aged 52, seen at the Royal Sussex County Hospital by Dr. W. A. Bourne, who made a diagnosis of disseminated sclerosis. A summary of his notes states that at that time he had for six months weakness of the arms and difficulty in walking, due to heaviness of the legs and a feeling that they did not belong to him, but there were no other paræsthesiæ and no bladder symptoms. Examination showed no abnormality of cranial nerves and a spastic weakness of all four limbs with absent abdominal reflexes and extensor plantar responses.

If reliance is placed only on clinical signs in these 3 cases, a diagnosis of a familial form of spastic paraplegia would appear probable. However, if consideration be given to the history in the first and third cases, it is

clear that relapses and sensory changes occurred in both during the course of their illnesses. Thus clinically the diagnosis of disseminated sclerosis seems justified in both these cases, being supported by the changes in the C.S.F. in the first case; by inference therefore the same can be said in the remaining case.

In one of our pedigrees (Family U, Appendix I) a diagnosis of disseminated sclerosis was made in 2 brothers and seemed probable in a paternal uncle, while in another branch of the family 3 brothers were affected by a progressive paraplegia. Unfortunately the available clinical details of these 3 brothers are extremely scanty, but are as follows:

Family U.—For family tree, *see* Appendix I, p. 226.

Case II.1.—W. J., born 1874, died 1912. At the age of 18 he developed a steadily progressive paralysis of the legs. Throughout his illness there was no involvement of the eyes or the arms, and bladder function remained normal. He apparently had no paræsthesiæ. There is no record of physical examination available from either St. Bartholomew's Hospital, which he attended as an outpatient at the age of 20, or the Northampton Hospital where he was an inpatient for 30 weeks. He committed suicide at the age of 38.

Case II.4.—H. J., born 1879, died 1939. This patient also developed paralysis of the legs at the age of 18 and the condition progressed without any remission until his death at the age of 60. It is stated that he was seen by Dr. Farquhar Buzzard of London in about 1914, and that a diagnosis of "spinal cord disease" was made. No detailed notes of his physical state are available.

Case II.8.—G. J., born 1890, died 1918. Onset of difficulty in walking at the age of 14, when he commenced to drag his legs and frequently fell. Until his death at the age of 28 the condition was steadily progressive and there was no involvement of cranial nerves or arms.

The onset during the second decade of a progressive paraplegia in three members of a family, without sensory symptoms, suggests a diagnosis of familial spastic paraplegia rather than disseminated sclerosis. The familial association of degenerative spinal cord disease and disseminated sclerosis was described by Brouwer (1939). He made a diagnosis of disseminated sclerosis in a girl aged 23 and of Friedreich's ataxia in two of her paternal aunts. In one of these aunts at post-mortem the diagnosis was proved to be Friedreich's ataxia and in the other disseminated sclerosis.

Discussion

The facts presented in this paper establish beyond any reasonable doubt that there is a small but nevertheless significant familial incidence of disseminated sclerosis. In his paper published in 1930 Brain suggested that the familial occurrence of this disease might be attributable to chance, common environment, or mutual infection. The figures here presented exclude chance as a factor and leave for discussion "common environment"

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or "mutual infection" as alternative explanations to a true genetic influence.

If "common environment" were an operative factor we should expect equally numerous examples of non-familial associated cases as of familial cases. It is possible that the incidence of the disease may be greater in some localities or communities than in others, but published evidence in support of this is scanty. Schaltenbrand (1939) saw 3 cases in a convent of 500, and Campbell *et al.* (1950) have recently reported the disease in 5 patients who attended the same school. However, in the small Stamford survey mentioned in this paper the evidence of direct contact between cases was negligible.

If "mutual infection" were the explanation of the familial incidence of disseminated sclerosis we would expect its occurrence more often in unrelated associates and in husband and wife; cases of marital disseminated sclerosis are rare. In one of our families the two affected relatives did not meet at any time during their lives (Appendix III, No. 7); Curtius (1933) records a similar fact, and in his case of two sibs who developed the disease Garcin (1936) observed that they had not met after the age of 3 months.

A detailed genetical analysis of the material presented in this paper and recorded in the literature will be reported in full by one of us (Pratt, 1951). In this section only the more important facts will be discussed.

The incidence of disseminated sclerosis in the parents of 310 patients was 3/620, and in the sibs of 168 patients was 6/538; these figures differ by a factor of approximately 2, and are compatible with a dominant mode of inheritance. Amongst our 33 pedigrees and those reported in the literature, a total of 217, both parent and offspring were affected in 51 instances. This finding is highly suggestive of the operation of a dominant gene. Only if the disorder were extremely common could the frequent affection of parent and offspring be compatible with transmission through a recessive gene. The occurrence of a disseminated sclerosis in three generations in one of our families (Family W) is overwhelmingly in favour of a dominant mode of inheritance in that particular family. If a dominant gene is responsible for the transmission of the disease, such a gene must have a very low manifestation, in view of the comparatively low familial incidence of the disease.

The incidence of first-cousin marriages amongst parents of patients with disseminated sclerosis has been recorded by Curtius (1933) three times in 106 patients, by Bell (1940) six times in 632 patients, and in the present series twice in 134 cases where specific inquiry was made.

The incidence in the three series combined is 11 in 872 (1·26 per cent), and differs significantly from the incidence in control populations, which was assessed by Curtius as 0·40 per cent and by Bell as 0·60 per cent. A parental consanguinity rate of this order would be found in a recessively determined character of an incidence of 1/1200 of the general population, if the material were homogeneous. However, the incidence of disseminated sclerosis amongst the sibs of patients (approximately 1/90) does not approach the incidence of 1/4 expected in a recessively determined disorder in which the gene is fully manifested, so that if a recessive gene is operative its manifestation must also be low.

In view of the evidence for both dominant and recessive modes of transmission it is probable that the material is not genetically homogeneous, and that different genes are responsible for producing the predisposition to the disease in different families.

However, a study of the sex of parent-offspring pairs in our cases and those in the literature (Appendix II) indicates that the problem may not be answered simply in terms of dominant or recessive inheritance. Parent-offspring pairs have occurred as follows:

Father — son ...	3	Mother — son ...	10
Father — daughter	11	Mother — daughter	27

It will be observed that there is a striking difference between the number of father-son pairs and the number of mother-daughter pairs which at first sight appears highly significant. There is, however, an unequal sex distribution of disseminated sclerosis in this country, female patients outnumbering males in a ratio of 3:2 (Brain, 1947). The overall sex ratio in familial cases of disseminated sclerosis presented in this paper and recorded in Appendix II is also 3:2 with an excess of females. The expected incidence of father-son pairs will therefore be less than that of mother-daughter pairs. It will also be less than that of father-daughter pairs. The occasional occurrence of impotence in males with disseminated sclerosis, whilst fertility in females is unaffected, might also tend to reduce the numbers of offspring of affected fathers compared with offspring of affected mothers.

In view of these factors, and the small numbers concerned, it is not possible to decide the significance of the sex distribution of parent-offspring pairs.

How important is the genetic factor in the ætiology of disseminated sclerosis? Heredity and environment play parts of varying importance in the causation of certain diseases. Heredity may be the only factor, as for example in brachydactyly, where all persons carrying the gene and none who lack it develop the disease, or environment may be the

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dominant factor, as for example in trauma, to which persons of any genetic constitution are liable. Commonly the two factors, heredity and environment, combine to produce disease. Theoretically a disease, determined mainly by environmental factors, might occur only in individuals of a certain genetic constitution: that is, the genetic background is essential. Alternatively individuals of any genetic constitution may be susceptible under the influence of appropriate environmental factors, those bearing certain genes being affected more readily. The facts presented in this paper are compatible with either hypothesis.

Heredity plays a part in some diseases which are determined largely by other factors. The familial occurrence of tuberculosis has long been observed, and Roberts (1940) has shown that this is not entirely due to environmental factors. When one of a pair of twins is affected with tuberculosis the probability of the other contracting the disease is higher in identical than in non-identical twins. Harris (1949) has found that diabetes mellitus occurs in about 5 per cent of the sibs of diabetics. Recently Doll and Buch (1950) have demonstrated a small but significant excess of observed over expected cases of peptic ulcer amongst the relatives of patients with that disease. An inherited tendency to develop allergic states, epilepsy, cancer, pernicious anæmia, hypertension, rheumatism and many other diseases has long been recognized.

There are thus a number of disorders of widely differing ætiology in which heredity plays some part; amongst these we believe disseminated sclerosis should now be placed. It is concluded that the ætiological factor or factors responsible for disseminated sclerosis may act more readily in the presence of an inherited disposition towards it.

Summary

(1) The slow recognition of a genetic factor in the ætiology of disseminated sclerosis has been due to a number of causes, including the low familial incidence, the lack of published material, and the difficulty in distinguishing the progressive form of disseminated sclerosis from familial spastic ataxia and paraplegia.

(2) 184 families in which more than one case of disseminated sclerosis occurred have been collected from the literature. In this paper a further 33 families are recorded.

(3) In a series of 168 consecutive cases of disseminated sclerosis seen by us during a period of eighteen months there were 12 instances of one or more relatives being similarly affected. In an earlier series of 142 patients, in which the inquiry was more limited, the family history was positive on 8 occasions. Therefore in a total of 310 cases the familial

incidence was 6·5 per cent. The case histories of affected members of families are recorded.

(4) The incidence of disseminated sclerosis in the sibs of 168 cases and in the parents of 310 cases is shown to be significantly higher than that expected on the basis of a random distribution of the disease.

(5) A few additional pedigrees of particular interest are described, including the occurrence of the disease in a mother and four of her daughters, and an example of the disease occurring by direct transmission in three generations.

(6) The clinical features and relative frequency of certain familial degenerative disorders of the spinal cord and of disseminated sclerosis are compared.

(7) The present study supports the view that a genetic factor is present in disseminated sclerosis, and that there is evidence pointing to both a dominant and a recessive mode of inheritance.

(8) A comparison is made between disseminated sclerosis and some other diseases in which a genetic factor plays a role in the ætiology. It is concluded that the ætiological factor or factors causing disseminated sclerosis may act more readily in the presence of an inherited disposition towards this disease.

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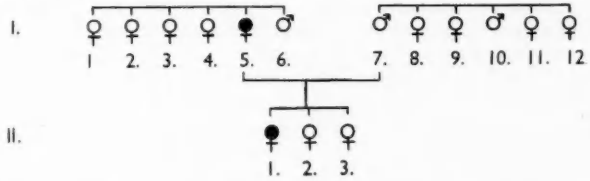
APPENDIX I.

CASE REPORTS.

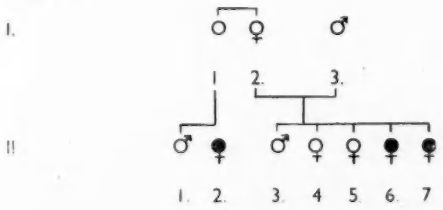
Family A.



Case II.1.—M. H., female, born 1909. Aged 33 during fourth and fifth months of pregnancy, heaviness and numbness L. leg below the knee, followed by dragging of leg; this remained until after birth of child. October 1945, aged 36, pain down L. leg, but examination (D. McA.) showed no neurological abnormality. February 1946, aged 36, numbness, dragging, and pins and needles L. leg, and pins and needles L. hand. Examination (D. McA.) showed: normal fundi, horizontal nystagmus; arms normal; absent abdominal reflexes; some weakness dorsiflexion L. ankle, R. plantar response equivocal, L. extensor, no sensory loss. C.S.F. protein 50 mg. per cent, Lange curve 0234332100. Almost complete remission with slight weakness of L. leg after exercise. Aged 38 R. leg became numb and stiff; this persisted for three months. Examination showed both plantar responses now equivocal, vibration sense absent R. leg diminished L. A complete remission followed. June 1949, aged 39, examination (N. D. C.) showed temporal pallor L. disc as a new sign, but the plantar responses were now flexor and vibration sensation had returned to the legs. She states that in October 1949 she lost the use of her R. hand for one week.

Case I.5.—R. L., female, born 1892. Aged 48 developed weakness both legs. 1.10.40 examination by Dr. L. R. Yealland at Prince of Wales Hospital showed normal cranial nerves and arms but a spastic paraplegia. Diagnosis of disseminated sclerosis made. She improved over one year, but aged 50 the R. leg suddenly became weak and she had pins and needles in both hands. Aged 51 developed incontinence of urine. Aged 55 commenced attacks of vertigo with falling to the L. Aged 57 weakness L. leg, which has persisted. Aged 58 weakness L. hand noticed for the first time. 4.4.49 examination Middlesex Hospital (N. D. C.) showed: normal cranial nerves; weakness and intention tremor L. arm with increased reflexes both arms, no sensory loss; abdominal reflexes diminished; spastic paraplegia more marked R. and L., extensor plantar responses, impaired postural sensation R. leg and absent vibration sensation both legs.

Family B.

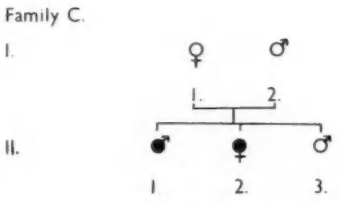


Case II.7.—L. H., female, born 1898, died 1948. April 1938, aged 39, pins and needles and numbness L. arm for one day. Aged 40 pins and

needles and numbness around L. knee for two weeks, followed by numbness of the big toe. Aged 41 sudden loss of sensation on hips and legs, followed soon after by weakness and loss of awareness of all her limbs and double vision. Almost complete remission; patient returned to work as a ward sister. Aged 43 relapsed with double vision, difficulty in writing, weakness of legs, after which condition steadily deteriorated. Aged 47 severe relapse with almost complete paralysis of all limbs; August 1945 inpatient London Hospital under care of Dr. G. Riddoch, who made a diagnosis of disseminated sclerosis. Examination then showed: normal cranial nerves apart from a defect in the temporal field L. eye; loss of power and diminished tone both arms, all reflexes in arms brisk and equal, loss of sensation to pin-prick, hot and cold, and vibration both arms; absent abdominal reflexes; marked loss of power both legs with brisk reflexes and extensor plantar responses, similar sensory loss to that in arms. Improved slightly. Aged 48 seen by one of us (D. McA.) when she had an established spastic paraplegia of moderate severity and an intention tremor in both arms. Killed aged 49 in a road accident when driving her wheelchair. No autopsy.

Case II.6.—M. H., female, born 1895, died 1940. Aged 24 transient attacks of giddiness and dragging of legs. 21.7.27, aged 32, admitted London Hospital under care of Dr. G. Riddoch. No details of physical state available; diagnosis of disseminated sclerosis made. Aged 35 readmitted following severe setback. Examination showed slight bitemporal pallor of discs, horizontal nystagmus, spastic paraplegia and an ataxic gait. Aged 39 readmitted London Hospital following recent difficulty in walking. Physical signs unchanged. After improvement relapsed three months later with increasing weakness L. leg and numbness of legs, also frequency of micturition. Examination then showed, in addition to previous signs, intention tremor of arms and loss of postural and vibration sensation in legs. There was no remission and she was admitted to the Putney Home for Incurables, where she died at the age of 45. No autopsy.

Case II.2.—M. W., female, born 1893. 1930, aged 37, onset of ataxia on walking with a subsequent remission and relapse. Aged 41 loss of visual acuity L. more than R.: this persisted; also numbness and stiffness of fingers. September 1941, aged 48, admitted Midland Nerve Hospital under care of Dr. A. V. Neale; walking was more difficult and she was unable to hold objects in her hands. Diagnosis of disseminated sclerosis made. Examination showed: pallor of both discs, bilateral choroidal degeneration, horizontal nystagmus; mild spastic paraplegia. C.S.F. showed protein 50 mg. per cent, Lange curve 0122100000. There was a partial remission, but since aged 56 there has been a gradual deterioration, and patient has become deluded.

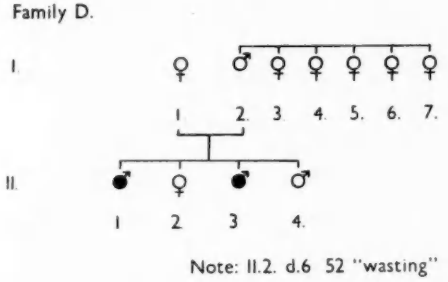


(Birth order unknown)

Case II.1.—W. L., male, born 1911. Aged 20 noted black spot in centre of field of vision R. eye for two months. Aged 21 double vision on looking to R., lasting three months, followed by weakness and numbness of legs. 15.3.33, aged 21, admitted Middlesex Hospital where examination (D. McA.) showed: pallor of both

discs, horizontal and vertical nystagmus; arms normal; slight weakness dorsiflexion R. foot, extensor plantar response R., equivocal plantar response L., vibration sense diminished both ankles. C.S.F. showed 35 mg. per cent protein, Lange curve 0001221100. Aged 23 weakness R. leg increased and both plantar responses became extensor. Over the next four years recurrent attacks of leg weakness. 26.10.38 examination (D. McA.) showed euphoria, pallor of both discs, nystagmus, intention tremor of arms with exaggerated reflexes, and an established spastic paraplegia with ataxia. Patient has not been seen since then, but his doctor states that his condition is stationary and he is able to walk with the aid of sticks.

Case II.2.—M. L., female, born 1912. Aged 15 blurring of vision and pain R. eye; recovery in three months. Aged 19 giddiness for one week, followed by blurring of vision with pain L. eye, and numbness L. leg and arm. 14.7.31 admitted Middlesex Hospital, aged 19. Examination (D. McA.) showed: visual acuity R. 6/6, L. 6/60, slight atrophy L. disc, no true nystagmus; arms normal except anæsthesia tips of fingers L. hand; diminution R. abdominal reflexes; exaggeration leg reflexes R. with an extensor plantar response, no sensory loss. C.S.F. showed 9 lymphocytes per c.mm., 50 mg. per cent protein, and a normal Lange curve. August 1949 she wrote that she was symptom free but since leaving hospital she had had occasional transient attacks of numbness and heaviness of R. leg.



Case II.1.—H. W., male, born 1902. Aged 34 incontinence of urine on four occasions. Aged 36 dimness of vision both eyes, R. more than L. Six months later dragging L. leg and numbness L. heel for three weeks. 9.12.38 admitted Middlesex Hospital, aged 36. Examination (D. McA.): euphoria, bitemporal pallor of discs, horizontal and vertical nystagmus; spastic weakness both arms, L. more than R., no ataxia or sensory loss; absent abdominal reflexes; severe spastic paraplegia, L. more than R., bilateral extensor plantar responses. C.S.F. contained 20 lymphocytes per c.mm., 35 mg. per cent protein, and Lange curve 0123443200. A good remission enabled him to return to work. Aged 44 weakness and loss of control R. leg. Examination showed signs as before but postural loss R. leg. Aged 47 blurring of vision, weakness L. arm. 10.5.49 examination (N. D. C.) showed following additional signs: intention tremor L. arm, postural loss R. arm, loss of postural sense both legs and of vibration sense below D6.

Case II.3.—C. W., male, born 1910, died 1936. Aged 22 loss of vision and weakness of legs. Aged 23 urgency of micturition and incontinence of urine with occasional retention. Steadily downhill course. Aged 25 only able to walk one mile. Aged 26 unable to stand: also noticed slurring of speech and tremor of arms. 1936 admitted National Hospital, Queen Square, under Dr. F. M. R. Walshe who diagnosed disseminated sclerosis. Examination showed: dysarthria, bitemporal pallor of discs, horizontal and vertical nystagmus; bilateral intention tremor; severe spastic paraplegia, bilateral extensor plantar responses, vibration loss

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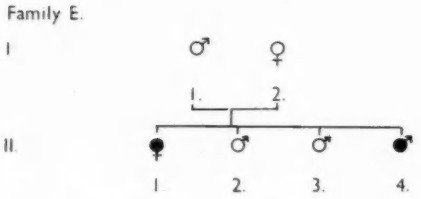
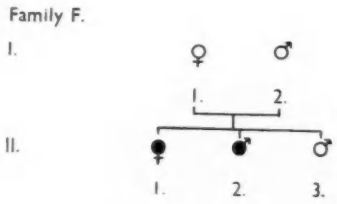
at ankles. C.S.F. normal. 1.4.36 transferred to North Middlesex Hospital where he died three weeks later. Histological examination of spinal cord confirmed diagnosis of disseminated sclerosis.



Case II.1.—D. B., female, born 1903. Aged 37 gradual loss of control of legs, precipitancy of micturition with occasional incontinence. Gradual deterioration. Aged 41 admitted Mount Vernon Hospital under Dr. P. Sandifer. C.S.F. normal, but no other clinical notes available. In 1946, aged 43, examination (D. McA.) showed: euphoria, bitemporal pallor of discs, horizontal nystagmus; intention tremor both arms; mild spastic paraplegia, more on R. than L., increased tendon reflexes, extensor plantar responses, cerebellar ataxia, loss of vibration sense. 1.12.48 Dr. Colin Grahame stated that there has been gradual deterioration; patient can walk indoors with difficulty.

Case II.4.—C. B., male, born 1911. Aged 18 transient paralysis L. arm. Aged 27 onset of difficulty in walking. Aged 35 seen by Dr. D. Kendall, Royal Sussex County Hospital, who found pallor of optic discs, gross bilateral intention tremor, and an advanced spastic paraplegia. Diagnosis of disseminated sclerosis made. Three months later had an attack of double vision. Aged 38 is reported as almost completely paraplegic and intensely euphoric. No record of lumbar puncture ever having been performed.



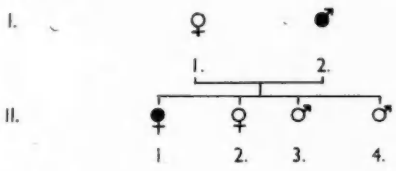
(Birth order unknown.)

Case II.1.—M. W., female, born 1894. Aged 45 noticed difficulty in typing with L. hand, due to clumsiness and numbness, followed by same symptoms R. hand. Aged 46 numbness and dragging L. leg. 30.12.41, aged 47, admitted Maida Vale Hospital under care of Dr. E. A. Blake Pritchard, who made a diagnosis of disseminated sclerosis. Examination showed: normal fundi except for arterio-sclerotic changes; normal power in arms but increased reflexes R. more than L., impaired sense of posture, light touch and pin-prick in tips of all fingers, and ataxia; abdominal reflexes feebly present; power diminished both legs with increased reflexes, R. more than L., R. plantar response extensor, L. doubtful, impaired sense of posture, light touch and pin-prick both feet. Blood pressure 200/120. C.S.F. normal, as was red blood cell count; normal gastric acidity. Condition steadily

deteriorated. Aged 51 admitted to New End Hospital. 21.6.46, aged 52, seen at Middlesex Hospital (D. McA.) when examination showed euphoria, nystagmus, and a moderate spastic paraplegia. March 1948 admitted to St. Benedict's Hospital, Tooting. 28.9.48 re-examination (N. D. C.) showed bitemporal pallor of discs, horizontal nystagmus, bilateral intention tremor, impaired postural sensation in fingers, absent abdominal reflexes and severe spastic paraplegia with loss of vibration sense in the legs. Aged 54 she had an attack of severe giddiness, followed by weakness of the L. arm, which improved in two weeks. Physical examination after this episode revealed no change.

Case II.2.—B. W., male, born 1897. August 1941, aged 45, transient weakness R. leg. Six months later seen at University College Hospital by Dr. F. M. R. Walshe, complaining of pain in legs on walking and occasional incontinence of urine and fæces. Examination showed nystagmus and a spastic paraplegia with loss of vibration sensation at ankles. C.S.F. contained 50 mg. per cent protein but was otherwise normal. Diagnosis of disseminated sclerosis made. Re-examination U.C.H. December 1943 showed exaggerated arm reflexes in addition to previous signs. Since then improvement in both walking and sphincter control. 13.7.49 examination (Dr. H. H. Wolff, U.C.H.) showed pallor temporal half L. disc, condition otherwise little changed.

Family G.



Case II.1.—M. T., female, born 1913. Aged 29 pins and needles both hands for some months. Aged 31 this symptom returned, also urgency and occasional incontinence of urine, followed in three months by dragging of R. leg. After a remission, symptoms returned and were associated with blurring of vision. 2.4.46 admitted Middlesex Hospital, aged 33. Examination (D. McA.) showed: fundi normal, horizontal nystagmus; slight weakness both arms with increased reflexes, no ataxia or sensory loss; abdominal reflexes absent; mild spastic paraplegia, bilateral extensor plantar responses, no sensory loss in legs. C.S.F. contained 60 mg. per cent protein, cells and Lange curve normal. 28.5.48, aged 35, additional weakness of arms and legs and incontinence of urine. Examination (N. D. C.): bitemporal pallor, horizontal nystagmus, marked spastic weakness of all four limbs with marked cerebellar ataxia, complete postural loss R. hand and both legs, and absent vibration sense to a level of D7.

Case I.2.—A. W. T., male, born 1888, died 1947. Aged 29 attack of weakness of legs. Such attacks recurred over the next four years. Aged 33 further attack without remission associated with incontinence of urine at times. 1927, aged 39, entered Star and Garter Home, Richmond, where a diagnosis of disseminated sclerosis was made by the late Dr. O. H. Woodcock. Details of physical state not available. Gradual deterioration until aged 58, unable to walk and doubly incontinent. He had transient attacks of diplopia and blurring vision. Examination at that time showed dysarthria, horizontal nystagmus, severe spastic paraplegia. C.S.F. not examined. Died aged 59. No autopsy.

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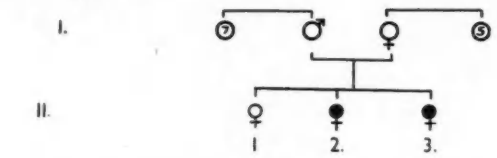
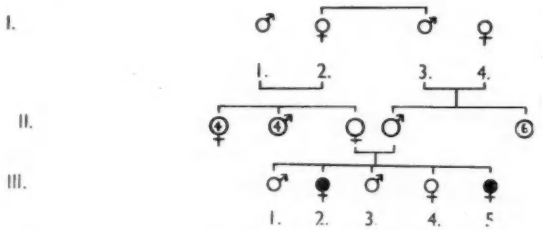
Family H.



Case II.3.—E. D., female, born 1896. Aged 23 weakness and numbness both legs, complete remission after four months. Aged 25 numbness below waist for two years. Aged 31 similar attack lasting three months. Aged 33 transient numbness and loss of power L. arm. Aged 38 weakness L. arm and leg, blurred vision L. eye, for three months. Aged 40 weakness and numbness L. leg. 8.3.38, aged 41, attended Middlesex Hospital. Examination (D. McA.): pallor L. disc, no nystagmus; increased reflexes both arms, bilateral intention tremor; absent abdominal reflexes; mild spastic paraplegia, extensor plantar responses, loss of vibration sense in legs. Aged 43 complete numbness below neck, and unable to walk. Aged 53, unable to read, severe paraplegia in flexion.

Case II.2.—G. D., female, born 1895, died 1938. Aged 13 paralysis one side of body, recovery in one month. Aged 17 weakness of one leg. During the following years recurrent attacks of weakness of arms and legs, and transient attacks of double vision. Seen at Middlesex Hospital aged 19, at National Temperance Hospital aged 27, and at Charing Cross Hospital aged 31. Unfortunately no notes can be traced. At each hospital parents were informed that the diagnosis was disseminated sclerosis. Death aged 43.

Family J.



Case III.2.—C. A., female, born 1896. Aged 39 L. sided hemiplegia with recovery in a few months. Aged 42 onset slowly progressive paraplegia. Aged 49 double vision for three months. Aged 51, sudden increase in paraplegia. January 1949, aged 53, admitted to Maida Vale Hospital. Examination (D. McA.): euphoria, dysarthria; bitemporal pallor of discs, horizontal and vertical nystagmus, exaggerated jaw-jerk; intention tremor both arms, normal power but exaggerated arm reflexes; absent abdominal reflexes; severe spastic paraplegia with extensor plantar responses, ankle clonus, cerebellar ataxia L. leg, absent postural sensation toes both feet. C.S.F. not examined.

Case III.5.—M. D., female, born 1899. Aged 32 tingling and pins and needles both feet for one month, recurring intermittently since. Aged 36 dragging of both feet, at first variable but since aged 45 constant and progressive. Urgency of micturition since aged 41. 25.6.49, aged 50, seen by Dr. Purdon Martin diagnosis disseminated sclerosis. 2.8.49 examination (D. McA.): normal discs, no nystagmus, slightly increased jaw-jerk; exaggerated arm reflexes; severe spastic paraplegia, R.

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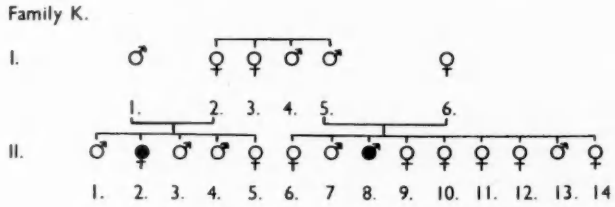
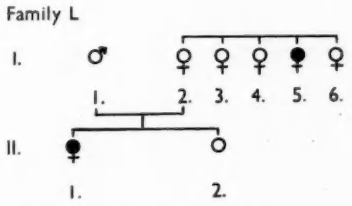
more than L., with extensor plantar responses, diminished vibration sensation R. leg, absent L. leg.



Case II.2.—P. B., female, born 1916. January 1949, aged 32, patches of burning sensation L. forearm and leg, lasting a few minutes. April 1949 cold sensation around L. abdomen for three days. May 1949 burning sensation L. abdomen which spread to involve hip and groin and was replaced ten days later by numb sensation in same distribution. One week later weakness L. leg. June 1949 burning sensation R. thigh. 29.7.49 admitted Middlesex Hospital. Examination (D. McA.): normal discs, no nystagmus; increased reflexes R. arm; abdominal reflexes depressed; slight weakness both legs, knee-jerks normal, ankle-jerks increased, plantar responses R. equivocal, L. extensor, over-reaction to pin-prick and hot and cold L. leg. C.S.F. normal except Lange curve 3321000000. Paræsthesiæ diminished in intensity whilst in hospital but since then have recurred intermittently.

Case II.8.—J. A., male, born 1909. Aged 31 blurred vision L. eye for twelve months. Aged 32 "electric sign" on flexing neck with transient weakness and numbness R. arm; July 1941 seen as outpatient Maida Vale Hospital by Dr. Russell Brain: examination showed pallor L. disc, increased jaw-jerk, diminished abdominal reflexes, impaired vibration sense in legs but flexor plantar responses. Symptom-free for twelve months. Aged 34 transient double vision. Aged 35 onset weakness of legs. Aged 37 weakness and numbness L. hand; 26.3.37 readmitted Maida Vale Hospital under Dr. Michael Kremer when the following additional signs were found: temporal pallor R. disc, horizontal nystagmus; intention tremor both arms, weakness L. arm with diminished reflexes and absent vibration sensation; spastic paraplegia with extensor plantar responses, cerebellar ataxia, loss of vibration sensation in legs and diminished appreciation to pin-prick and cold below D7. C.S.F.—8 cells per c.mm., 45 mg. per cent protein, Lange curve 3222211100. After discharge some improvement at first, but aged 39 he relapsed with urinary and fæcal incontinence and has been bedridden ever since.



Case II.1.—J. B., female, born 1823. Aged 14 tingling and numbness whole of R. side, followed by R. hemiplegia. Admitted St. Bartholomew's Hospital under Dr. D. Denny Brown, who found R. spastic hemiparesis, maximal in the arm; no sensory abnormality. C.S.F. cells 8 per c.mm., otherwise normal. Provisional diagnosis cerebral aneurysm, subsequently revised to disseminated sclerosis. Com-

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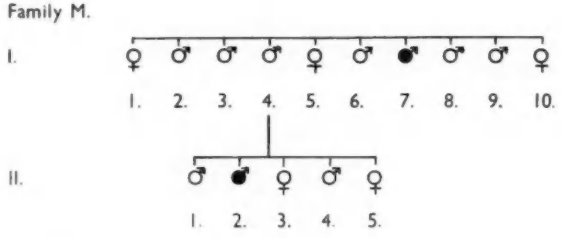
plete remission after two months. Aged 21 attacks of pins and needles and weakness R. side of a few days' duration, also blurring of vision R. eye for six weeks, followed by blurring of vision L. eye for four weeks. Aged 24 legs became stiff and unsteady on walking and blurred vision returned. 13.5.48, aged 24, admitted Middlesex Hospital. Examination (D. McA.): bitemporal pallor of discs, horizontal and vertical nystagmus; intention tremor both arms with increased reflexes; absent abdominal reflexes; spastic paraplegia with extensor plantar responses, impaired postural and vibration sensation both feet. C.S.F. protein 45 mg. per cent. Lange test not performed. Since discharge some improvement. 13.10.49 examination (N. D. C.) showed complete pallor L. disc but otherwise no change.

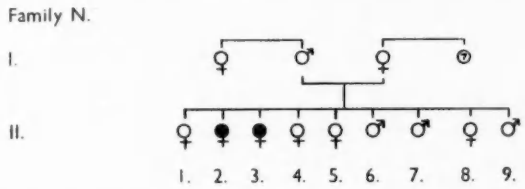
Case I.5.—E. S., female, born 1903, died 1926. Aged 21 double vision, slurred speech, tremor R. hand, dragging R. leg and urgency of micturition. Some spontaneous improvement before admission to London Hospital June 1924, under care of Dr. Lewis Smith. Examination showed R. pupil larger than L. (no record of disc appearance), nystagmus in all directions; weakness and intention tremor of arms; spastic paraplegia. Improved after discharge but relapsed and was readmitted, when physical findings were unchanged except for increase in severity of paraplegia. Died one year later. No record of C.S.F. examination.



Case I.7.—J. F., male, born 1895. Aged 51 pins and needles L. leg. One month later weakness and dragging L. leg and occasional incontinence of urine. Paræsthesiæ disappeared but leg weakness persisted. Aged 53 weakness L. hand. 6.8.49 admitted Middlesex Hospital, aged 54. Examination (D. McA.): bitemporal pallor of discs, horizontal nystagmus; spastic weakness L. arm and hand with some wasting, absent supinator and biceps jerks, increased triceps jerk, no ataxia, absent vibration sensation both hands; absent abdominal reflexes; severe spastic weakness L. leg, increased knee and ankle jerks R. and L., bilateral extensor plantar responses, vibration sense absent in legs and trunk. C.S.F.: normal cell count, 40 mg. per cent protein, negative W.R., Lange curve 4555310000.

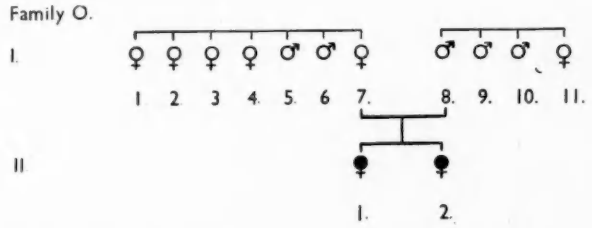
Case II.2.—D. F., male, born 1934. Aged 15 after one month of general malaise, headache and low-grade fever, became unsteady on his feet, and following fall off a bicycle was unable to stand unsupported, and feet were numbed; 7.1.49 admitted Haymeads Hospital under Dr. E. Leiper. Examination showed normal cranial nerves and arms, a mild paraplegia with increased leg reflexes and ankle clonus, extensor plantar responses, ataxia of L. leg, but no sensory loss. C.S.F. showed 75 lymphocytes per c.mm., 48 mg. per cent protein; Lange curve not performed. By 22.1.49 the R. arm was completely paralysed; this recovered in about two weeks. A diagnosis of ? acute disseminated encephalomyelitis, ? acute disseminated sclerosis was made. The case was then transferred to the London Hospital under the care of Dr. Russell Brain. 4.2.49 examination showed the following abnormal signs: L. lower facial weakness; hypotonia of arms with ataxia on the R. and increased reflexes; normal power in legs but reflexes increased R. more than L., both plantar

responses extensor; doubtful loss of postural sense in L. toes. There was rapid spontaneous improvement. A final diagnosis of disseminated sclerosis was made.



Case II.3.—B. M., female, born 1906. Aged 39 pins and needles and numbness L. leg for three weeks. Aged 40 numbness L. side of body for three weeks. Aged 41 numbness L. side recurred for three weeks, followed by blurring of vision R. eye for three months. At this time double vision for one day. November 1947 aged 41 admitted National Hospital, Queen Square, under Sir Charles Symonds, who made a diagnosis of disseminated sclerosis. After discharge, weakness and loss of sensation R. arm; complete remission for six months. Aged 42 weakness L. leg for two months, followed by pain and blurring of vision L. eye. Three months later recurrent weakness of legs, pins and needles. 27.8.49 aged 42 admitted Middlesex Hospital. Examination (D. McA.): bitemporal pallor of discs, no nystagmus; increased reflexes in arms, slight hypalgesia to pin-prick both hands; abdominal reflexes absent; weakness both legs, increased reflexes and extensor plantar responses, postural loss both legs and vibration loss to a level of D8. C.S.F. contained 6 lymphocytes per c.mm., 50 mg. per cent protein, and Lange curve 2443321000.

Case II.2.—K. B., female, born 1902. Aged 38 dragging of R. leg on walking. Aged 42 onset of urgency of micturition. Aged 46 increasing weakness R. leg, also weakness R. arm. 4.10.48, aged 46, admitted Charing Cross Hospital under care of Dr. R. A. Hickling. Examination: fundi normal, R. lateral rectus palsy, horizontal nystagmus, R. facial weakness, dysarthria; marked spastic paresis R. arm, bilateral intention tremor; absent abdominal reflexes; spastic paraplegia, absent vibration sensation R. leg, bilateral extensor plantar responses. No record of C.S.F. available. There was some improvement during her stay in hospital. A diagnosis of disseminated sclerosis was made.



Case II.1.—E. M. P., female, born 1910. Aged 33 unsteadiness on walking for three months, also momentary blurring of vision in either eye. Since then recurrent attacks of tingling in either arms or legs, and attacks of blurred vision in one eye lasting about a week and clearing spontaneously. May 1949, aged 39, attack of tingling in hands and feet, the feet clearing in ten days, the hands persisting. 17.5.49 examination (N. D. C.): pallor on both discs, no nystagmus; arms normal power, reflexes increased R. more than L., no ataxia, loss of postural sense in fingers, R. more than L.; abdominal reflexes absent on R.; legs normal power and

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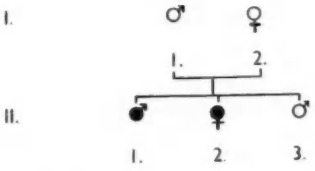
tone, reflexes increased R. more than L., plantar responses equivocal, diminished vibration sensation R.

Case II.2.—K. M., female, born 1920. Aged 15, dimness of vision, pins and needles and weakness of legs; complete recovery from this attack. 9.4.36, aged 16, seen by Dr. (later Sir) Leonard Parsons, who diagnosed disseminated sclerosis. Examination showed pallor of optic discs, nystagmus, increased reflexes in all limbs, R. plantar response extensor. One year later bilateral extensor plantar responses and impaired vibration sense at the ankles. Her sister, Case II.1, states that since then she has had recurrent attacks of blurring vision, weakness of legs, pins and needles, and giddiness. We have no record of recent re-examination.

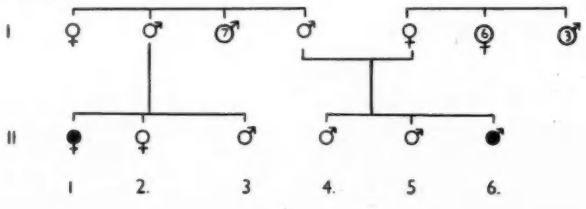
Family P.



Case II.1.—F. P., male, born 1914. Aged 28, defect of central vision for two weeks. Aged 31, "bubbling" sensation both legs after exercise, lasting five months. Tingling in feet on neck flexion. Aged 32, feeling of irritation L. side of neck and shoulder for one month. Aged 33, weakness L. leg with marked recovery in three months, followed by difficulty in identifying objects in R. hand, blurring of central vision R. eye, and "shingles" L. chest. February 1949, aged 34, further weakness L. leg and tingling in hands. 23.5.49 admitted Middlesex Hospital. Examination (D. McA.): bitemporal pallor of discs, nystagmus on R. lateral gaze; power and tone normal in arms, intention tremor R more than L., arm reflexes diminished, absent postural sensation fingers R. hand, and diminished vibration sense both arms; absent lower abdominal reflexes; spastic-ataxic paraplegia, with bilateral extensor plantar responses, normal postural sense, vibration sense diminished R. and L. C.S.F. not examined. 10.1.50 examination (N. D. C.) showed return of postural sensation in R. hand, otherwise state unchanged. A few weeks later developed double vision lasting five days.

Case II.2.—J. D., female, born 1917. Aged 31, weakness L. hand and leg with tingling in legs on neck flexion; 2.3.49 admitted Connaught Hospital under care of Dr. Stewart Wallace, who made a diagnosis of disseminated sclerosis. Examination showed no cranial nerve abnormality, weakness of L. arm and leg with bilateral extensor plantar responses, and loss of pain sensitivity in the R. leg. C.S.F. was normal. During her stay in hospital she made a complete recovery except for the appearance and persistence of tingling in the fingers.

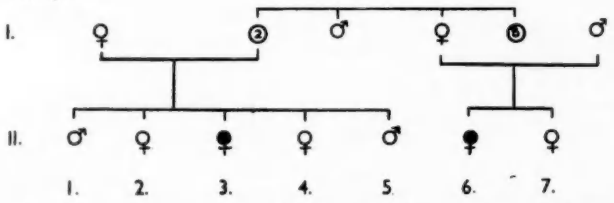
Family Q.



Case II.6.—R. R., male, born 1908. Aged 35, pins and needles R. arm, spreading to R. trunk and leg, weakness and clumsiness R. hand; recovery in three months. Aged 38, transient pins and needles R. hand and further clumsiness which has persisted. Three months later weakness R. leg after exercise, variable but has persisted. 23.5.49, aged 41, seen by one of us (D. McA.). Examination showed: temporal pallor L. disc, rotatory horizontal nystagmus, increased jaw-jerk; incoordination R. hand, increased reflexes R. arm; spastic paresis R. leg with bilateral extensor plantar responses, spastic ataxic gait, no sensory loss. C.S.F. not examined.

Case II.1.—S. J., female, born 1896. Aged 37, blurring of vision R. eye, recovery slow and incomplete. Aged 40, further attack in R. eye, central scotoma found by Mr. Maurice Whiting. Aged 42, atrophy R. optic disc noted by Mr. Whiting, vision R. 6/12, L. 6/6 with glasses. Aged 46, numbness and clumsiness R. arm and sense of constriction round wrists and ankles. 23.2.42 examination by Dr. F. G. Hobson showed pallor R. disc, R. facial weakness; paresis R. arm with increased reflexes, intention tremor and some postural loss; moderate spastic paraplegia, bilateral extensor plantar responses. Complete recovery in four months. Aged 49, seen by Dr. Worster-Drought, who found considerable improvement, no paresis but still increased reflexes in R. arm and leg and extensor plantar response on R. Patient now states that her only symptom is occasional pins and needles in the hands.

Family R.



Case II.3.—D. W., female, born 1907. Aged 35, L. sided "sciatica" which recurred twice during the next four years. Aged 39, dragging R. leg on walking. 1947, aged 40, admitted Royal Sheffield Hospital under the care of Dr. James Carson, who made a provisional diagnosis of disseminated sclerosis. He found a moderate paraplegia with increased reflexes, R. more than L., and bilateral extensor plantar responses. C.S.F. was normal. Aged 41, L. leg stiff and weak after exercise, pins and needles R. arm and cold sensation around abdomen. 14.4.49, aged 42, seen Middlesex Hospital. Examination (D. McA.): fundi normal, no nystagmus; increased reflexes both arms, bilateral intention tremor; abdominal reflexes absent; spastic paraplegia more marked R. than L., bilateral extensor plantar responses, diminished vibration sensation to level D7.

Case II.6.—M. W., female, born 1902, died 1939. Aged 21, numbness across abdomen, tingling in hands. One month later weakness L. leg, followed by weakness R. leg and hands, occasional incontinence of urine. December 1923, aged 21, admitted National Hospital, Queen Square, under care of late Dr. Risien Russell, who made diagnosis of disseminated sclerosis. Examination showed emotional lability, bitemporal pallor of discs, nystagmoid jerks to R., postural loss in fingers, absent abdominal reflexes, spastic paraplegia with vibration loss at ankles. Partial remission during stay in hospital. Aged 23, relapsed with increased difficulty in walking and uselessness of R. hand. Readmitted National Hospital, where signs were unchanged except for horizontal nystagmus. Further remission, but relapsed aged 26 when re-examination at National Hospital showed, in addition, bitemporal pallor, bilateral intention tremor, and a severe spastic paraplegia. Patient died aged 37.

Family S. *See text.*

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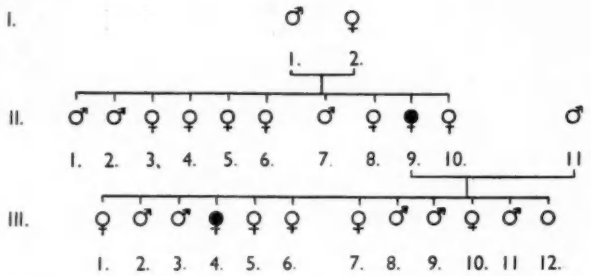
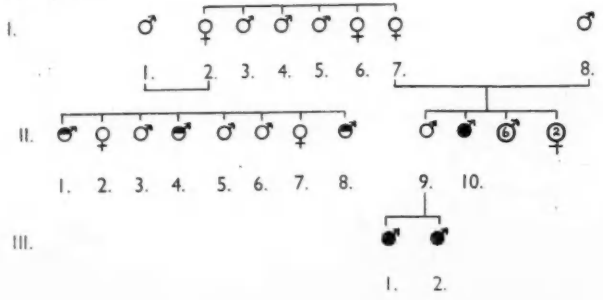
Family T.



Case III.4.—L. G., female, born 1902. Aged 45, gradual onset dragging R. leg, leading to severe weakness in six months; numbness R. arm and leg, and double vision. Partial remission. Aged 46, noticed vibration down the back on neck flexion; 28.7.48 admitted Middlesex Hospital under Dr. M. Kremer. Examination showed normal fundi, diplopia on upward movement, horizontal and vertical nystagmus, hypalgesia to pin-prick over first and second division R. cr. V.; weakness both arms with increased reflexes; absent abdominal reflexes; moderate spastic paraplegia, vibration loss both ankles. C.S.F. normal. A good remission followed. March 1949, aged 48, walking again deteriorated, particularly in the dark, with frequent falls. November 1949 following a fall developed numbness L. face; L. upper arm and thigh felt stiff and numb, and toes tingled. Within three days unable to walk. Readmitted Middlesex Hospital. Examination (D. McA.): cranial nerves as before except over-reaction to pin-prick L. face; weakness both arms, increased reflexes R. more than L., impaired co-ordination L. more than R., over-reaction to pin-prick and cold L. arm, trunk and leg; mild spastic paraplegia, R. more than L., bilateral extensor plantar responses, marked cerebellar ataxia especially L. leg, slight loss light touch L. foot, vibration loss both feet. A rapid and marked remission again resulted.

Case II.9.—E. R. C., female, born 1877. Aged 17, admitted mental hospital with acute mania, followed by loss of power R. arm and leg for six months. Aged 37, attack of dragging R. leg. Three further attacks in next twenty years with complete remission; during attacks pins and needles R. arm. Since age 57 slight constant dragging R. leg. Now aged 72, only additional symptom precipitancy of micturition. 10.11.49 examination (R. T. C. P.): pallor temporal half R. disc, no nystagmus; increased reflexes both arms, R. more than L., but no paresis; spastic weakness both legs, R. more than L., extensor plantar responses, diminished vibration sense both ankles.

Family U.



Case III.2.—A. M., male, born 1914. Aged 16, sudden double vision lasting three to four months. Aged 18, dragging of L. leg, with gradual improvement, so that by May 1933, aged 19, walking was normal, but symptoms recurred in 1937 and persisted. Aged 26, weakness both hands, and later dragging of R. leg. Gradual deterioration until admission to Middlesex Hospital 12.8.49, aged 35, when examination (D. McA.) showed: euphoria, bitemporal pallor R. more than L., no nystagmus; spastic paresis both arms, R. more than L., bilateral intention tremor; absent abdominal reflexes; severe spastic paraplegia with bilateral extensor plantar responses, complete loss of postural sense, and vibration sense loss to a level of D5.

Case II.1.—W. M., male, born 1907, died 1949. Aged 28, gradual onset heaviness and weakness L. leg, with improvement. Age 30 pins and needles both legs; September 1937 admitted to London Hospital under care of Dr. Russell Brain. Examination showed euphoria, slight pallor temporal half L. disc; arms normal apart from brisk reflexes; absent abdominal reflexes; spastic weakness both legs, L. more than R., reflexes increased L. more than R., bilateral extensor plantar responses, vibration loss both ankles, slight postural loss L. big toe. C.S.F. normal. Diagnosis disseminated sclerosis. Patient not examined since 1937, but widow states that he gradually deteriorated and latterly became incontinent. Died suddenly 13.7.49.

Case II.10.—J. M., male, born 1877, died 1943. Aged 38, onset of double vision, which cleared, but attacks recurred over the next nine years. On 9.6.24, aged 47, admitted to Northampton General Hospital, complaining of double vision since 1915, poor grip, and difficulty in walking, so that he had given up work twelve months previously. No detailed record available, but hospital summary states he showed nystagmus and an early spastic paraplegia. Leg weakness progressed, and he was admitted to St. Mary's Hospital, Kettering, in May 1943, and died there on 28.7.43. It was noted that he had scanning speech and a spastic paraplegia.

APPENDIX II

TABLE I. GROUP I. DIAGNOSIS OF DISSEMINATED SCLEROSIS ACCEPTED, DETAILS GIVEN IN ORIGINAL PAPERS. (Chronological Order)

Author	*Reference*	*Relationship of cases of D.S.*
Cestan, R., and Guillain, G. (1900)	*Rev. Médecine*, **20**, 813	Brother and sister
Reynolds, E. S. (1904)	*Brain*, **27**, 163	Sister and 2 brothers; 2 sisters
Eichhorst, H. (1913)	*Med. Klinik*, **9**, 1617	Female, her daughter and son
Maier, C. (1947)	*Schweiz. Med. Wschr.*, **77**, 697	
Hoffmann, J. (1913)	*Dtsch. Z. Nervenheilk.*, **47**, 247	Sister and brother (twice)
Röper, E. (1913)	*Mschr. Psychiat. Neurol.*, **33**, 56	2 brothers
Schob, F. (1913)	*Neurol. Zbl.*, **32**, 1547	Brother and sister
(1922)	*Z. ges. Neurol. Psychiat.*, **80**, 56	
Abrahamson, I. (1915)	*J. nerv. ment. Dis.*, **42**, 295	Female and her son
Curschmann, H. (1917)	*Z. ges. Neurol. Psychiat.*, **35**, 330	Male and his paternal aunt
(1920)	*Dtsch. Z. Nervenheilk.*, **66**, 225	

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Author	*Reference*	*Relationship of cases of D.S.*
Schultze, F. (1919)	*Dtsch. Z. Nervenheilk.*, **63**, 257	Sister and brother
Kramer (1921)	*Z. ges. Neurol. Psychiat.*, **25**, 232	2 sisters
Haber, T. (1922)	*Mschr. Psychiat. Neurol.*, **51**, 226	2 sisters
Albrecht, L. (1923)	*Arch. Psychiat. Nervenkr.*, **69**, 268	Sister and brother
Leri, A. (1924)	*Rev. neurol.*, **31**, i, 788	Female and her 2 daughters
Obständer, E. (1926)	*Mschr. Psychiat. Neurol.*, **61**, 350	Female and her daughter; brother and sister; male and female cousins; 2 sisters
Allen, C. E. (1927)	*Lancet*, **2**, 701	Sister, brother, sister
Simon, A. (1927)	*Z. ges. Neurol. Psychiat.*, **109**, 555	Male, female third cousins once removed; male first cousins; sister and brother; 2 sisters; 2 brothers; female and her daughter
Redlich, E. (1928)	*Wien. med. Wschr.*, **78**, 932	2 brothers; 2 sisters twice
André-Thomas (1929)	*Rev. neurol.*, **36**, ii, 714	Female and her daughter
Allison, R. S. (1930)	*Brain*, **53**, 391	2 sisters
Krebs, E., and Chavany, J.-A. (1930)	*Rev. neurol.*, **37**, i, 188	Sister and brother
Lotmar, R. (1922)	*Schweiz. med. Wschr.*, **3**, 1146	2 sisters; 2 brothers; 2 sisters; brother and sister; male and his daughter; female, her son and daughter; 2 male cousins; male and female cousins; female and her daughter
Bing, R., and Reese, H. (1926)	*Schweiz. med. Wschr.*, **7**, 30	
Ackermann, A. (1931)	*Schweiz. med Wschr.*, **12**, 1245	
Bing, R. (1932)	*Schweiz. med Wschr.*, **13**, 1069, 1093	
Bing, R. (1932)	*Schweiz. med. Wschr.*, **13**, 1069, 1093	2 brothers
Burns, M. A. (1932)	*Arch. Neurol. Psychiat. Chicago*, **28**, 1446	Male and his daughter
Jossman (1932)	*Z. ges. Neurol. Psychiat.*, **61**, 260	Brother and sister
Marburg, O. (1932)	*Jb. Psychiat. Neurol.*, **48**, 303	Female and her daughter; 2 sisters, their maternal aunt and maternal grandmother; female and her 2 daughters
Curtius, F. (1933)	Multiple Sklerose und Erbanlage. Leipzig, Georg Thieme	Sister and brother; female cousins once removed; male and female first cousins; male and female second cousins

Author	*Reference*	*Relationship of cases of D.S.*
Klieneberger, O. (1933)	*Dtsch. Z. Nervenheilk.*, **130**, 299	2 sisters and a brother
Janota, O. (1933)	*Cas. Lék. ces.*, 1281	2 sisters
Legras, A. M. (1933)	*Z. ges. Neurol. Psychiat.*, **144**, 198	Monozygotic male twins
Astwazaturow, M. (1935)	*Z. ges. Neurol. Psychiat.*, **153**, 744	Dizygotic male twins
Ellermann, M. (1935)	*Rev. neurol.*, **64**, 668	2 brothers
Laignel-Lavastine, and Koressios, N. T. (1935)	*Rev. neurol.*, **64**, 914	Female and her 2 sons
Fortuyn, J. D. (1935)	*Ned. Tijdschr. geneesk.*, **79**, ii, 1812	3 brothers
Garcin, R. (1936)	*Rev. neurol.*, **65**, 58	Brother and sister
Dereux, J., and Pruvost, A. (1936)	*Rev. neurol.*, **65**, 351	2 sisters
Ledoux, E. (1936)	*Bull. Soc. méd. Hôp. Paris*, 640	Brother, sister, brother
Thums, K. (1936)	*Z. ges. Neurol. Psychiat.*, **155**, 185	Male and female twins
Jentsch, F. R. (1937)	*Dtsch. Z. Nervenheilk.*, **145**, 144	Monozygotic male twins
Matzdorff, P. (1937)	*Dtsch. med. Wschr.*, **63**, ii, 1513	Female cousins; female and her daughter; sister and brother
Stransky, E. (1937)	*Wien. Klin. Wschr.*, **50**, i, 328	Male and daughter
Steiner, G. (1938)	*J. nerv. ment. Dis.*, **88**, 42	2 sisters
Curschmann, H. (1938)	*Dtsch. Z. Nervenheilk.*, **145**, 225	3 brothers
Isenschmid, R., and Olloz, M. (1939)	*Schweiz. med. Wschr.*, **20**, 267	Monozygotic male twins
Wellach, H. (1939)	*Z. ges. Neurol. Psychiat.*, **164**, 392	2 half-brothers
Benedek, L., and Horanyi-Hechst, B. (1942)	*Dtsch. Z. Nervenheilk.*, **154**, 40	Brother and 2 sisters; sister and brother
Spiegel, L. A., and Keschner, M. (1943)	*Arch. Neurol. Psychiat. Chicago*, **50**, 706	Sister and brother
Schaltenbrand, G. (1943)	Die Multiple Sklerose des Menschen. Leipzig, Georg Thieme	Brother and sister
Arasa, F. (1946)	*Medicina Clinica Barcelona*, **6**, 146	Sister, brother, sister
Millar, J. H. D. (1949)	*Lancet*, **2**, 556	Sister and brother; brother, sister and her daughter; sister and brother
Mackay, R. P. (1950)	Proc. Assoc. Research Nervous and Mental Dis., p. 150. Baltimore, Williams and Wilkins	3 brothers; 4 times in sibs

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TABLE II. GROUP II. DIAGNOSIS OF DISSEMINATED SCLEROSIS ACCEPTED, DETAILS OF ONLY ONE CASE GIVEN IN ORIGINAL PAPERS

Author	*Reference*	*Relationship of cases of D.S.*
Klausner, I. (1901)	*Arch. Psychiat. Nervenkr.*, **34**, 841	Brother and sister twice
Frey, K. (1922)	*Schweiz. med. Wschr.*, **3**, 1084	Sister and brother
Gerson, M. (1922)	*Dtsch. Z. Nervenheilk.*, **74**, 251	2 sisters
Obständer, E. (1926)	*Mschr. Psychiat. Neurol.*, **61**, 350	Brother and sister
Herrmann, G. (1928)	*Z. ges. Neurol. Psychiat.*, **114**, 804	2 sisters
Dreyfus, G. L., and Mayer, K. (1929)	*Dtsch. Z. Nervenheilk.*, **111**, 68	Male and his son
Ackermann, A. (1931)	*Schweiz. med. Wschr.*, **12**, 1245	Brother and 2 sisters
Curtius, F. (1933)	Multiple Sklerose und Erbanlage. Leipzig, Georg Thieme	Male first cousins, once removed
Haug, K. (1934)	*Mschr. Psychiat. Neurol.*, **88**, 225	Male and his son
Williams, D. (1946)	*Proc. R. Soc. Med.*, **39**, 599	Monozygotic female twins
Campbell, A. M. G., Daniel, P., Porter, R. J., Russell, W. Ritchie, Smith, H. V., and Innes, J. R. M. (1947)	*Brain*, **70**, 50	Brother and sister

TABLE III. GROUP III. DIAGNOSIS OF DISSEMINATED SCLEROSIS ACCEPTED, DETAILS NOT GIVEN IN ORIGINAL PAPERS

Author	*Reference*	*Relationship of cases of D.S.*
Erb, W. (1878)	Handbuch der Krankheiten des Nervensystems, 2nd Ed. Part I, p. 86. Leipzig.	Hereditary transmission (twice); brother and sister (twice)
Brissaud (1902)	*Arch. Neurol. Paris*, **14**, 535	2 brothers
Berger, A. (1905)	*Jb. Psychiat. Neurol.*, **25**, 168	Patient and brother (twice); patient, sister and father
Batten, F. E. (1909)	*Proc. R. Soc. Med.*, Vol. II, Part 2, Neurology, 35	2 members of a family
Collier, J. (1909)	In discussion following paper by Batten (1909)	2 members of a family several times
Roeper, E. (1913)	*Mschr. Psychiat. Neurol.*, **33**, 56	2 brothers
Oppenheim, H. (1914)	*Dtsch. Z. Nervenheilk.*, **52**, 169	2 sibs on 3 occasions

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Author	*Reference*	*Relationship of cases of D.S.*
Bramwell, B. (1917)	*Edinb. med. J., N.S.*, **18**, 96	2 sisters; sister and brother; female and daughter; female and son
Bauer, J. (1921)	Die Konstitutionelle Disposition zu inneren Krankheiten. Berlin, Julius Springer, p. 182	Male first cousins once removed
Davenport, G. B. (1922)	Multiple Sclerosis, Association for Research in Nervous and Mental Diseases, Vol. II (1921) New York, Hoeber	Female and her son
Wechsler, I. S. (1922)	*Arch. Neurol. Psychiat. Chicago*, **8**, 59	Female and her son; brother and sister (twice)
Schob, F. (1930)	*Klin. Wschr.*, **9**, ii, 1565	Female and her daughter
Haenel, H. (1930)	*Klin. Wschr.*, **9**, ii, 1565	2 sibs
Bing, R., and Reese, H. (1926)	*Schweiz. med. Wschr.*, **7**, 30	2 sibs; 2 sisters; female and her son
Bing, R. (1932)	*Schweiz. med. Wschr.*, **13**, 1069, 1093	
Adie, W. J. (1932)	*Brit. med. J.*, **2**, 997	2 sisters
Curtius, F. (1933)	Multiple Sklerose und Erbanlage, Leipzig, Georg Thieme	2 brothers (twice); 2 female first cousins and a female second cousin; brother and sister
Astwazaturow, M. (1935)	*Z. ges. Neurol. Psychiat.*, **153**, 744	Female and her father
Curtius, F., and Speer, H. (1937)	*Z. ges. Neurol. Psychiat.*, **160**, 226	Female and child; brother and sib; monozygotic male twins
Steiner, G. (1938)	*J. nerv. ment. Dis.*, **88**, 42	First cousins
Curtius, F. (1939)	Handbuch der Inneren Medizin, Mohr, L. and Staehelin, R., 3 Auflage, V. 2, p. 1358. Berlin, Julius Springer.	10 times in sibs; twice in parent and child; one more distant relationship
Wilson, S. A. Kinnier (1940)	Neurology, Vol. I, p. 152, London, Edward Arnold	Twice in 2 sisters
Winther, K. (1941)	*Nordisk. medicin*, **11**, 2229	3 times in sister and brother
Sällström, T. (1942)	*Acta med. Scand.*, Suppl. 137	4 times in sisters; 5 times in brothers; 6 times in sister and brother; female and her father; female and her mother

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Author	*Reference*	*Relationship of cases of D.S.*
Schaltenbrand, G. (1943)	Die Multiple Sklerose des Menschen. Leipzig, Georg Thieme	Mother and son; brother and sister; twice in sibs; male, his son and daughter, and his sister and her granddaughter
Steiner, G. (1949)	Personal communication	2 sisters 3 times; brother and sister 3 times; 2 brothers (twice)
Thums, K. (1949)	Personal communication	Monozygotic twins

APPENDIX III

The following additional familial instances of disseminated sclerosis have been encountered outside the two groups presented in this paper.

1. Three brothers.
2. Two sisters—twice.
3. Brother and sister.
4. Male and his daughter—twice.
5. Female and her daughter.
6. Female and her maternal uncle.
7. Two female cousins (mothers were sibs).
8. Two female cousins (fathers were sibs).

AN EXPERIMENTAL STUDY OF THE HIPPOCAMPAL CONNEXIONS OF THE CINGULATE CORTEX IN THE RABBIT

BY

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Introduction

Interest in the connexions of the cingulate cortex has greatly increased in recent years following the demonstration of autonomic effects from electrical stimulation of area 24 in the monkey (Smith, 1945). Ablation of area 24 in the monkey is reported to result in profound changes in behaviour characterized by an increased tameness and loss of "social conscience" (Ward, 1948). The neural pathways involved in these physiological and psychological effects are complex. Bard and Mountcastle (1948) have studied the role of the olfactory bulb and tubercle, the amygdala, the hippocampus and the cortex of the pyriform lobe (the "rhinencephalon" of earlier workers), and the cingulate cortex in the expression of rage and the suppression of angry behaviour in cats. Their results, while conflicting with those of Bucy and Klüver in the monkey, suggest that the amygdala acts as a funnel through which inhibitory influences from the limbic cortex, the neocortex and the amygdala itself exert a suppressing action on brain-stem mechanisms. Interest has recently centred on the possibility of a circular pathway interconnecting the hippocampus, the mammillary body, the anterior thalamic nucleus, and the cingulate cortex, and finally returning to the hippocampus through the cingulum.

Some of the anatomical pathways interconnecting the limbic cortex and the rhinencephalic structures are well known. Thus, from the hippocampus the fornix system carries impulses to the mammillary body whence they are relayed to the anterior nucleus of the thalamus. From the anterior nucleus a rich projection terminates in the cingulate[2] gyrus (Le Gros Clark and Boggon, 1933). More recently Rose and Woolsey

[1]This work was carried out during the tenure of a Nuffield Foundation Dominion Travelling Fellowship in Medicine.

[2]In order to avoid phonetic confusion, the term "cingulate" has been used throughout this paper in preference to the term "cingular," which is used by some other authors including Rose and Woolsey.

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(1948), in an experimental study in the rabbit and cat, have shown that there is a precise topographical projection from the three main parts of the anterior thalamic nucleus to the cingulate cortex, and they have subdivided this region accordingly into an anterior limbic region, a cingulate area and a retrosplenial area. The large size of the cingulate and retrosplenial areas in the rabbit makes it particularly suitable for a study of the connexions of this region of the cortex.

This study has aimed at the determination of connexions between the anterior cingulate, posterior cingulate and retrosplenial areas and the hippocampal formation. The method of Glees (1946) has been used to show the presence of degenerating fibres and terminals after cortical ablation. Strychninization studies of the retrosplenial area in the macaque suggest the possibility of such connexions (Pribram, Lennox and Dunsmore, 1950). Cajal described afferent fibres to the hippocampus from three main sources: from the entorhinal areas of the same and opposite sides and through the supracallosal striæ. He considered these fibres as third order olfactory tracts, and assigned a principally olfactory function to the hippocampus. This is now largely discounted (Brodal, 1947), and an alternative explanation has been suggested that the hippocampus may be intimately concerned in a mechanism for the maintenance of emotional stability.

Material and Methods

Under intravenous nembutal anæsthesia, the cingulate cortex was exposed by separation of the cerebral hemispheres. Lesions in the cortex were made by careful excision with a Graefe knife or by coagulation with a diathermy needle. Lesions produced with the knife were more satisfactory as they tended to spread less beyond the margins of the incision than with the diathermy needle. Bleeding was controlled by fibrin foam. Penicillin powder was dusted lightly on the exposed brain and the wound closed with skin sutures.

The animals were allowed to survive for a period of three to six days and then killed with intravenous nembutal. They were immediately perfused with 4 per cent formol saline and the brain removed. After further fixation in formol saline, frozen sections were cut from each brain at a thickness of 15 μ and stained by the Glees silver technique. Corresponding sections were also cut at 25 μ for Weil and Nissl staining to allow accurate identification of the level of section. In different brains with comparable lesions sections were cut both sagittally and coronally in order to obtain as complete a picture as possible of fibre degeneration.

The survival time was varied slightly in different animals, depending on whether maximal degeneration in the terminals or in the fibres was

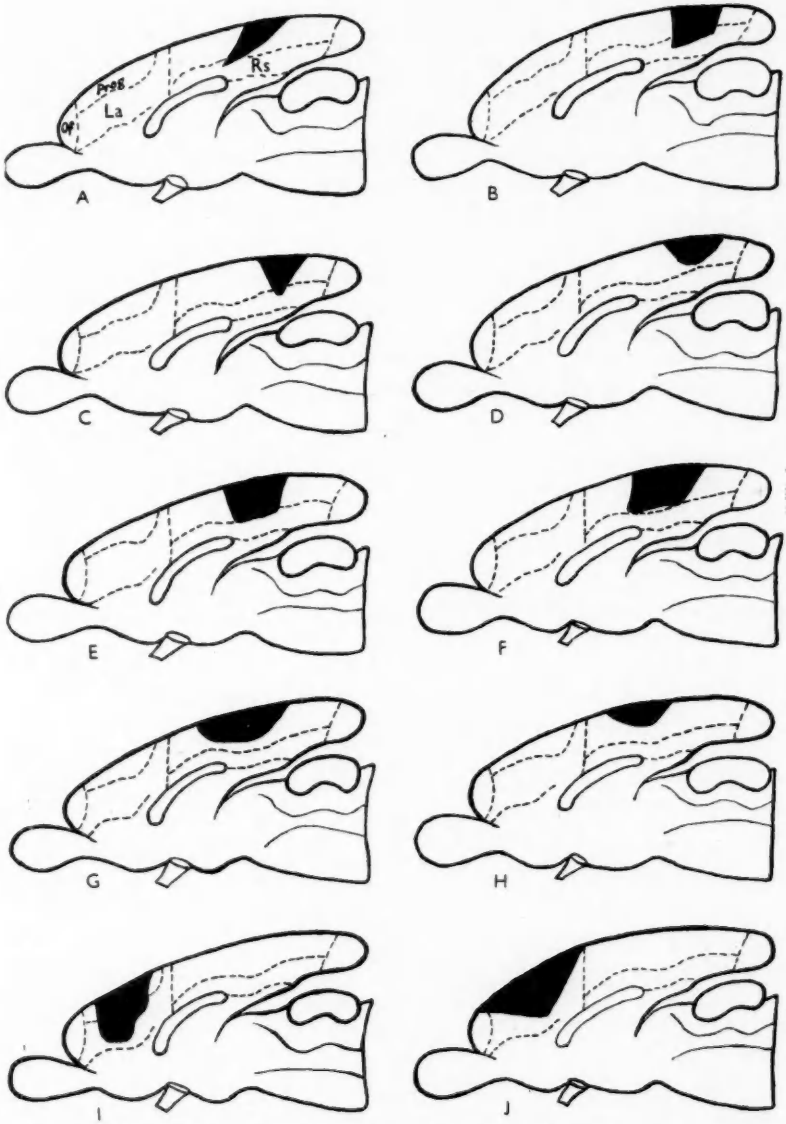

FIG. 1.—Diagrams illustrating the extent of the lesions in the anterior cingulate, posterior cingulate and retrosplenial areas in the cerebral hemisphere used in this study. Hemispheres A, B, C, D, I and J were sectioned sagittally. Hemispheres E, F, G and H were sectioned coronally. Resulting degeneration was observed in each hemisphere at the following sites: A, B, C and D in the presubiculum and dentate gyrus, E, F, G and H in the presubiculum and subiculum, I and J in the cingulum, posterior cingulate cortex, presubiculum and subiculum. The cortical areas are defined thus (after Rose and Woolsey): *Cg* = cingulate area. *Le* = anterior limbic region. *Of* = orbital-frontal region. *Prag* = precentral agranular area. *Rs* = retrosplenial area.

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desired. The factors affecting the rate of appearance of varicose terminals and degenerated fibres have been discussed by M. Meyer (1950).

Ten hemispheres were used in this study. Eight had lesions in the posterior cingulate and retrosplenial areas, and in two the lesion was in the anterior cingulate area. A number of normal series of sections stained by the Nissl and Weigert methods were used for comparisons with the experimental material (fig. 1).

Experimental Results

(1) *Connexions of the Posterior Cingulate and Retrosplenial Areas.*

Of the eight hemispheres with lesions in these areas, four were cut coronally and four sagittally.

(*a*) *Connexions with the subiculum and presubiculum.*—The fibre pathways running from these areas towards the hippocampus are most clearly seen in coronal sections through the posterior part of the cerebral hemisphere a little behind the splenium of the corpus callosum (fig. 2).

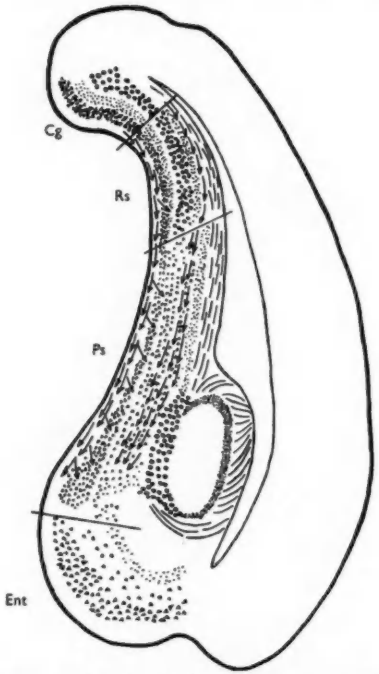

Fig. 2.—Coronal section of a hemisphere with a posterior cingulate ablation showing paths of degenerating fibres to the presubiculum and subiculum. The superficial and deep pathways indicated by arrows are sharply separated. *Cg*= posterior cingulate area. *Rs*=retrosplenial area. *Ps*=presubiculum above passing gradually into the subiculum below. *Ent*=entorhinal area.

At this level, the medial wall of the hemisphere is made up of several cortical areas. Superiorly is a small portion of the posterior cingulate area, which passes inferiorly into the retrosplenial area. The presubiculum and subiculum jointly occupy about half the medial wall of the hemisphere at this level. The delineation of the limits of the subiculum in this region is difficult owing to the gradual transition into the presubiculum on the one hand and the prosubiculum on the other. Lorente de Nó (1934) has pointed out that, in the human brain at least, if the prosubiculum and the presubiculum are considered as special fields, to differentiate a subiculum is arbitrary. There is a sharp division at the lower border of the subiculum marking it off from the entorhinal area, which extends as far laterally as the rhinal fissure. In the diagram of a section in this region the lowest part of the hippocampal formation is seen projecting into the lateral ventricle.

Four hemispheres (figs. 1, E, F, G, H) were examined by coronal section at this level, and the contralateral hemisphere in one of these cases was used as a control. The extent of the lesion in each case is shown in fig. 1. The degenerating fibres follow two clearly defined paths inferiorly into the presubiculum and subiculum. Medially, immediately under the surface of the cortex, is a moderately dense plexus of fine fibres which run the whole length of the medial wall of the hemisphere as far as the lower border of the subiculum. Here, just above the junction with the entorhinal area, it ceases abruptly. The fibres in this layer show heavy degeneration (Pl. I, fig. 1), and in the pyramidal cell layer immediately subjacent to this plexus many swollen terminals are visible (Pl. I, fig. 2). Degenerating fibres extend inferiorly to the lower end of the plexus adjacent to the entorhinal area.

A second, more deeply placed, pathway also connects the posterior cingulate area with the subiculum and presubiculum. In coronal sections behind the corpus callosum and passing through the lower posterior part of the ammonshorn, the degenerating fibres lie in the upper part of their course deep to all the layers of the retrosplenial cortex, while laterally they are in contact with the densely packed fibres of the alveus in the ventricular wall. In the presubicular region this deep pathway shows relatively few degenerating fibres, but inferiorly, particularly at the level of the ammonshorn, fine degenerating fibres are numerous. They form a broad band considerably wider than the superficial pathway at this level, lying in laminæ IV and V of the subicular cortex as defined by Lorente de Nó (1934). Varicose terminals are numerous adjacent to the cell bodies in these deeper layers.

(*b*) *Connexions with the dentate gyrus.*—In sagittal sections it is possible to trace degenerating fibres from the posterior cingulate and retrosplenial areas into the superior part of the dentate gyrus. They

are not numerous, but in the four hemispheres (fig. 1, A, B, C, D) examined by sagittal section the distribution of the degenerating fibres was very similar in each case (fig. 3A). The degeneration is found mainly in the plexiform layer superficial to the densely packed pyramidal cells of the dentate gyrus. The degenerating fibres are in the region of the maximum convexity of the pyramidal cell layer. A few degenerating fibres are also found in the plexiform layer deep to these pyramidal cells. The presubiculum also shows degeneration in its zonal layer and in the vicinity of the pyramidal cells of layer II. The distribution of the degeneration in the presubiculum and dentate gyrus resembles closely the arrangement of the "perforant" or direct temporo-ammonic tract of Cajal (1911) which he believed to terminate partly in the presubiculum, and partly in the dentate gyrus by crossing the hippocampal fissure. The question of cortico-dentate connexions will be dealt with more fully later.

(*c*) *Commissural connexions.*—In each of the four hemispheres examined by coronal section, a large fascicle of closely grouped fibres could be seen to enter the splenium of the corpus callosum. The fibres are heavily degenerated, and confined mainly to the dorsal part of the splenium (Pl. I, fig. 3). They can be traced from the floor of the lesion in the upper part of the cingulate cortex and reach the corpus callosum by skirting around the cingulum. The latter appears as a bundle of large fibres placed in the angle between the cingulate cortex and the corpus callosum. In the opposite hemisphere the degenerating fibres pass into the cingulate cortex and thus appear to constitute a cortico-cortical commissural bundle. Their precise termination in the contralateral cingulate cortex could not be determined, however, as this cortex invariably showed slight damage from manipulation of the adjacent hemisphere during the operation. However, the degenerating bundles passed only in the direction of the contralateral cingulate cortex and may be presumed to function as commissural bundles between the homologous areas.

(2) *Connexions of the Anterior Cingulate Area.*

The effects of lesions in the anterior cingulate area were examined in two hemispheres. In each case the lesion damaged the upper part of the anterior cingulate area only, and involved to a considerable extent the frontal agranular cortex lying superior to the anterior cingulate area on the medial wall of the hemisphere.

(*a*) *Connexions with the subiculum and presubiculum.*—M. Meyer and Allison (1948) have previously noted degeneration in the cingulum of the rabbit following lesions in the anterior cingulate cortex. They traced the degenerating fibres to the region of the presubiculum. The

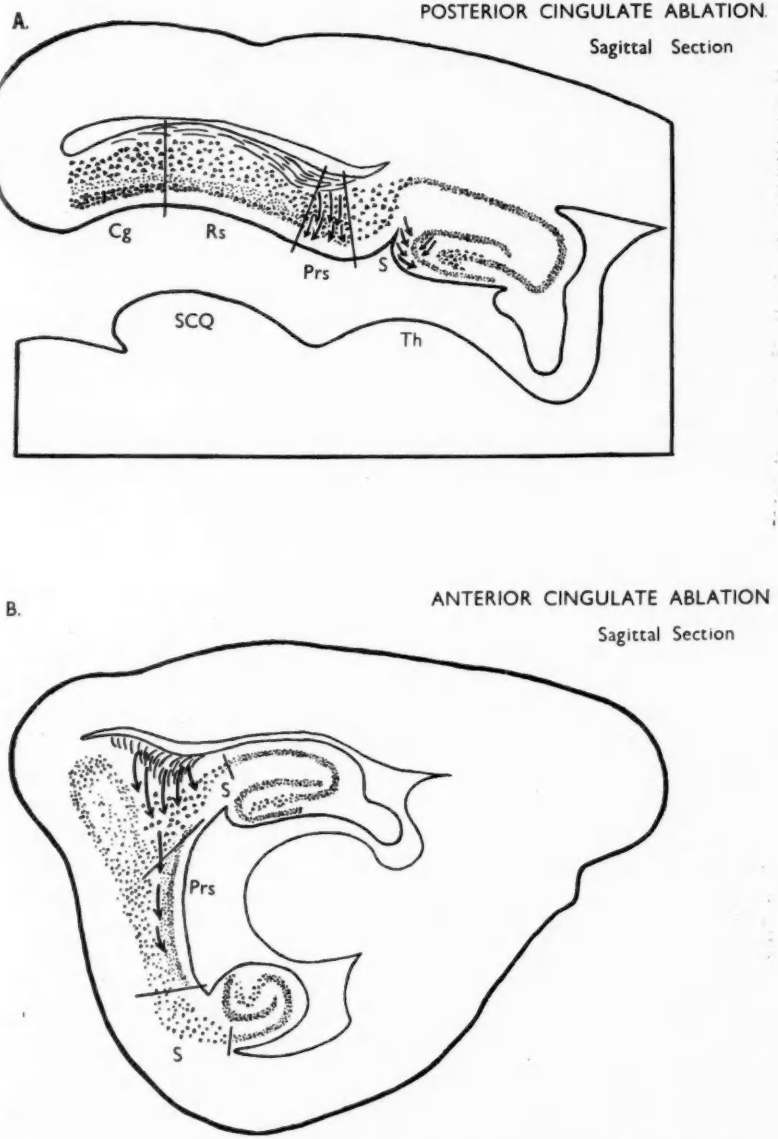

FIG. 3A.—Course of degenerating fibres in the presubiculum and dentate gyrus following a posterior cingulate ablation. 3B.—Course of degenerating fibres of the cingulum to the subiculum and presubiculum following an ablation of the anterior cingulate region. *Cg* = posterior cingulate area. *Rs* = retrosplenial area. *Prs* = presubiculum. *S* = subiculum. *S.C.Q.* = superior corpus quadrigeminum. *Th* = thalamus.

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two hemispheres (fig. 1, I, J) used in the present study confirm their results.

In sagittal sections close to the median plane, a large fibre bundle is seen running antero-posteriorly along the dorsal surface of the corpus callosum. In the silver sections the fibres composing it are seen to vary considerably in size, many of those in the more dorsal part of the bundle being quite large. Anteriorly the bundle clings closely to the dorsal surface of the corpus callosum, but as the splenium is approached the bundle fans out and turns ventrally around the splenium, enclosing it superiorly and posteriorly. Sagittal sections cut farther from the median plane show the fibres of the cingulum in a position ventral to the splenium of the corpus callosum. They run inferiorly in this region towards the cells of the subiculum and presubiculum (fig. 3B).

In medial sagittal sections of the experimental material, degenerating fibres are seen running postero-inferiorly from the lower margin of the anterior cingulate lesion towards the corpus callosum where they join the cingulum, and the degeneration involves both large and medium-sized fibres (Pl. I, fig. 4). The degenerating fibres curve around the splenium of the corpus callosum and then run towards the cells of the subiculum and presubiculum (Pl. I, fig. 5). Swollen terminals are present in considerable numbers around the cells of the upper part of the subiculum but are scanty in the middle and lower Parts (Pl. I, fig. 6). Degeneration could not be traced into the dentate gyrus and ammonshorn.

(*b*) *Connexions with the posterior cingulate area.*—Examination of that portion of the cingulum lying dorsal to the posterior third of the corpus callosum shows degenerating fibres leaving it to run upwards towards the posterior cingulate cortex. A careful study of this posterior cingulate cortex shows degenerating terminals in the layers I and IV. Almost no degeneration could be seen amongst the large pyramidal cells of layers II and III. Thus the cingulum contains short cortico-cortical association fibres as well as the longer bundles reaching the subiculum. This point is significant in the comparative anatomy of the cingulum and is discussed more fully later.

(*c*) *Some physiological effects noted after cortical ablation.*—It was constantly noticed during the anterior and posterior cingulate ablations that a marked increase in rate and depth of respiration occurred at the moment of removing the strip of cortex and persisted for ten to twenty minutes after completion of the ablation. This effect was noted even though the lesion was entirely unilateral. The effect on pulse-rate and blood pressure was not recorded.

An interesting alteration in behaviour was observed in a rabbit in which the upper part of the anterior cingulate cortex had been ablated in both hemispheres. Prior to operation this animal displayed the usual

timid disposition. When removed from its cage on the third day after operation and placed in the middle of the room, it squealed loudly and continuously and thumped its hind-limbs on the ground as though in rage. It ran slowly around the room in an aimless fashion until restrained. This behaviour recurred whenever the animal was removed from the cage until it was killed on the fifth day. The brain showed extensive degeneration in the cingulum in each hemisphere. No changes in behaviour were noted in any of the other animals, including one with a large bilateral ablation of the posterior cingulate and retrosplenial areas. Motor weakness in the limbs was not seen in the cases of anterior cingulate ablations.

Discussion

The architectonic subdivision of the cortex on the medial aspect of the cerebral hemisphere was first studied on a comparative basis by Brodmann (1909). He distinguished cingulate and retrosplenial areas in this region of the cortex in all mammals. Brodmann further subdivided the cingulate region into an anterior agranular region which includes areas 24, 25 and 32, and a posterior granular division consisting mainly of area 23. He described the retrosplenial region as forming chiefly area 29. It has a granular cortex and in the rabbit he subdivided it into areas 29 a–e. Brodmann considered that the cingulate region differentiates considerably in the primates, while the retrosplenial region is greatly reduced. He found that in rodents, however, the retrosplenial region is highly developed. M. Rose (1928), from a comparative study of this region, differed in his conclusions from those of Brodmann in that he was unable to find a posterior cingulate granular division in rodents, insectivores and marsupials. More recently, J. Rose and Woolsey (1948) have studied the subdivision of the limbic cortex (i.e. the cortex receiving projections from the anterior nuclei of the thalamus) in the rabbit and cat. They used the method of retrograde degeneration following cortical ablation, and concluded that each of the three major portions of the anterior thalamic nucleus project to separate regions of the medial cortex. They subdivided this cortex accordingly into an anterior limbic region, a cingulate area and a retrosplenial area, the latter two regions having a granular cortex (fig. 4A).

A comparison of the orthogonal reconstruction of Rose and Woolsey with Brodmann's map for the rabbit indicates that Brodmann's areas 29a and b correspond to Rose and Woolsey's retrosplenial area, while areas 29 c and d correspond to the latter's cingulate region. Brodmann pointed out that the retrosplenial region occupies one-tenth of the whole cortical area in the rabbit and one three-hundredth in man. The lesions

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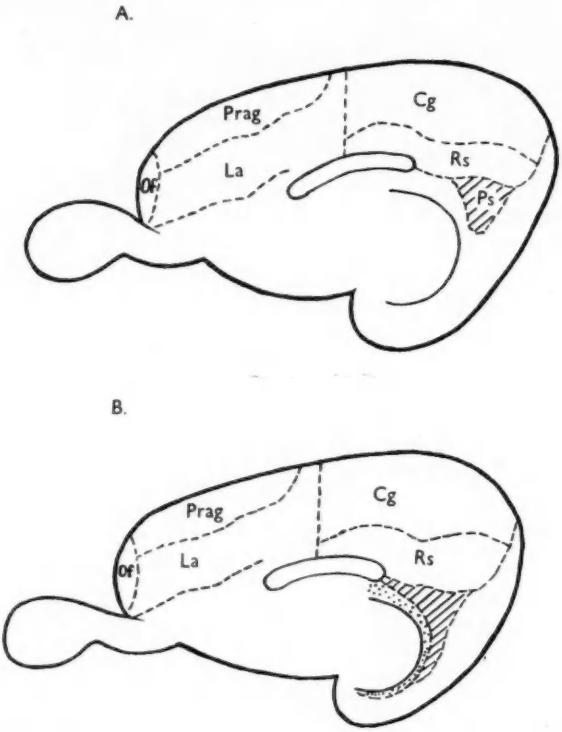

FIG. 4A.—Orthogonal reconstruction of the medial aspect of the cerebral hemisphere, after Rose and Woolsey, showing the size of the "post-subicular area" (Ps) which corresponds largely to the presubiculum of this study. 4B.—Extent of the presubiculum (shaded) and subiculum (stippled) taking into account those parts of the presubiculum which are obscured by the retrosplenial and entorhinal areas in an orthogonal reconstruction.

in our experiments have been made in the cingulate area and the upper part of the retrosplenial area as defined by Rose and Woolsey.

Examination of our own serial Nissl and Weigert material indicates agreement with the architectural subdivision of the cingulate and retrosplenial areas of Rose and Woolsey. The presubiculum, however, which appears to correspond largely to their "post-subicular area," is considerably more extensive than indicated in their orthogonal reconstruction. They point out that the orthogonal method produces considerable distortion in this area. It is partly concealed above by the overhanging retrosplenial cortex, and inferiorly by the upward projection of the entorhinal area. In sagittal and transverse sections, however, it can be traced as far forward as the plenium of the corpus callosum, and is easily

differentiated from the more dorsally situated retrosplenial cortex, principally by its thinner supragranular layers, the absence of small granule cells and in the parallel arrangement of the cells in layer V in horizontal rows. Sagittal Weigert sections show numerous fibres entering its deep aspect to run towards the surface. These fibres are not present in the adjacent retrosplenial field and their course resembles that of Cajal's perforating temporo-ammonic tract. This area also appears to extend inferiorly beyond the limits indicated by Rose and Woolsey, running as a strip which follows the curve of the ammonshorn to its postero-inferior limit (fig. 4B).

A careful study following lesions in the posterior cingulate region did not disclose any terminal degeneration in the anterior thalamic nuclei. Damage to cortico-thalamic neurons at their origin in the cortex would have been expected to produce terminal degeneration around the cells of the thalamus easily visible with the Glees silver method after the survival periods used. The pathways between the posterior cingulate region and the anterior thalamic nuclei described by Rose and Woolsey thus seem to be efferent from the thalamus, and no good evidence has been found in this study to support the concept of a reciprocal cortico-thalamic pathway. The retrograde axonal degeneration and disappearance of cells which occur in the thalamus as a late effect of the cortical ablation appears not to have progressed to a significant extent in the first few days following the cortical ablation.

In the cases with the anterior cingulate ablations, degenerating fibres could be seen joining the cingulum inferior to the lesion and then curving around the genu of the corpus callosum. This matter will be discussed more fully later, but it should be pointed out that Cajal (1911) described such fibres in the rat and rabbit and considered that they reach the corpus striatum. There is no evidence in the present study of their termination in the anterior thalamic nuclei.

Loo (1931) has described in considerable detail the archipalæopallial association fibres of *Didelphys*, grouping them in three main pathways: cingular palæo-ammonic fibres which curve around the posterior angle of the lateral ventricle and then run forward to enter the cingulum ammonale; alvear palæo-ammonic fibres which arise in the pyriform cortex and cross the first group at a sharp angle; and thirdly the fasciculus cortico-dentatus of Zuckerkandl (1903), a diffuse system of unmyelinated fibres which arise with the second group and pass directly into the dentate gyrus. The fasciculus cortico-dentatus also contains two additional groups of fibres, one group curving around the posterior poles of the hemisphere to the medial side, and the other formed of fibres from the retrosplenial cortex. Obenchain (1925) noted a similar arrangement

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of cortico-dentate fibres in the South American marsupial *Caenolestes.* Abbie (1942) described in the Australian marsupial *Perameles nasuta* fibres running from the ventricular angle to cross the hippocampal fissure and reach the dentate gyrus. He noted the resemblance to the course of the perforating or direct temporo-ammonic tract of Cajal.

The distribution of the degenerating cortico-dentate fibres after posterior cingulate lesions follows closely the course of the perforating temporo-ammonic tract of Cajal (1911). He believed that this tract arises in the "posterior superior temporal cortex" (or entorhinal area of Brodmann) and terminates in the presubiculum and also in the dentate gyrus, reaching the latter by crossing the hippocampal fissure. The fibres from the posterior cingulate cortex following this course in the experimental material form only a small portion of the whole tract, since many normal fibres are seen running with the degenerating fibres both in the presubiculum and the dentate gyrus. The small proportion of the degenerating fibres in this instance in relation to the number of normal fibres raises the problem of the significance of the degeneration seen in these experiments. It is obviously important to decide in each case whether the amount of the degeneration indicates damage to a major pathway between various areas, and, in those cases where the degenerating fibres run in close association with the more numerous normal fibres, the possible source of these normal fibres is also worth consideration. One great advantage of the experimental method employed in the present investigation is that it permits the elucidation of the course of comparatively small bundles of fibres in the midst of much larger groups.

In these experiments, the superficial and deep pathways from the posterior cingulate cortex to the presubiculum and subiculum (fig. 2) are formed of numerous fibres almost all of which are degenerated. The pathway is thus an important one and clearly arises mainly in the posterior cingulate region. On the other hand, the cortico-dentate fibres from this region constitute only a small proportion of the perforant temporo-ammonic tract (fig. 3A). Most of the fibres of this tract appear to come from the upper part of the entorhinal area in the manner described by Cajal (1911). The degeneration in the cingulum after an anterior cingulate ablation affects nearly all the large fibres and many of the smaller ones, and this can therefore be regarded as an important pathway from the anterior cingulate region to the presubiculum and subiculum. The number of degenerating fibres and terminals in the posterior cingulate cortex after such a lesion, however, is small. The callosal degeneration in posterior cingulate ablations affects severely the majority of the fibres in the dorsal part of the splenium.

The only previous experimental study of the hippocampal connex-

ions of the cingulate cortex is that of Probst (1903) in cats and dogs using the Marchi method. He found degeneration as far back as the hippocampus in anterior sections of the cingulum of the cat and dog. The cingulum remained intact, however, if the section involved the hippocampal cortex or ammonshorn, and also in lesions of the olfactory bulb and motor cortex. He thus concluded that the fibres of the cingulum going to the hippocampal cortex arise from the cingulate cortex.

Dejerine, quoted by Cajal (1911), showed the presence of commissural fibres in man interconnecting the cingulate cortex on each side through the corpus callosum. Cajal stated that he was unable to find similar callosal fibres in his studies of the smaller mammals. The presence in our material of degenerating fibres in the corpus callosum is therefore significant.

Cajal (1911) gives a very clear account of the structure and connexions of the cingulum as seen in his Golgi preparations. He found that in the mouse and rabbit it has two distinct portions, internal and external, that the inner bundle is the homologue of the human cingulum and is formed of thick fibres, and that the lateral band is equivalent to the superior longitudinal fasciculus. The true cingulum contains, as well as the short association bundles connecting adjacent regions of the cingulate cortex, a very long tract running its whole (or almost its whole) length. He also states that the cingulum contains three groups of fibres arising from the cells of the limbic cortex: posterior fibres running back to the splenium of the corpus callosum and the "cortex of the occipital pole" (retrosplenial area); anterior fibres which run to the genu of the corpus callosum and then turn downwards towards the anterior and of the corpus striatum where they enter the projection pathways, and thirdly, bifurcating fibres which divide near their origin to run both anteriorly and posteriorly. Those fibres which run back to the splenium of the corpus callosum were considered by Cajal to enter both the subiculum and the ammonshorn.

In our experimental material degeneration after anterior cingulate lesions was severe in the large medial fibres of the cingulum and terminal degeneration was present in the posterior cingulate cortex. Terminal degeneration was also present in the subiculum and presubiculum, being most severe in its upper part, but scanty in the middle and at the lower end. Contrary to Cajal's findings, degeneration could not be traced into the ammonshorn.

Pribram, Lennox and Dunsmore (1950) have recently stimulated area 24 in the macaque, using the method of strychnine neuronography. They found only restricted local firing at all times, with no responses from the posterior cingulate and retrosplenial areas. M. Meyer (1950), however,

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has found terminal degeneration in the presubiculum of the macaque following ablation of area 24. A. Meyer, Beck and McLardy (1947), relying on gliosis studies in human leucotomy material, traced degeneration in the cingulum not further than 3 cm. behind the cut. Beck (1950) has given renewed attention to the problem in more extensive material, and has traced the gliosis throughout the length of the cingulate gyrus to the level of the splenium but could not demonstrate degeneration on the hippocampal region.

Summary

(1) An experimental study has been made in the rabbit of the connexions of the limbic cortex with the hippocampal region, using the silver staining method of Glees to demonstrate degenerating fibres and terminals following cortical ablation.

(2) It has been found that there is a strong connexion from the posterior cingulate and retrosplenial areas to the subiculum and presubiculum. The fibres run as two distinct laminæ vertically downwards through the substance of the presubicular and subicular cortex. The superficial weaker lamina is situated in the outermost layer of the cortex. The broader and deeper lamina shows numerous degenerating terminals in the presubicular and subicular cortex.

(3) Following lesions in the posterior cingulate and retrosplenial cortex degenerating fibres can be seen in sagittal sections in the upper part of the presubiculum and the upper part of the dentate gyrus. Their course to the dentate gyrus and presubiculum resembles closely that of the perforating temporo-ammonic tract of Cajal.

(4) A commissural connexion between the posterior cingulate and retrosplenial regions of one side and the corresponding regions of the opposite side has been demonstrated passing through the dorsal part of the splenium of the corpus callosum.

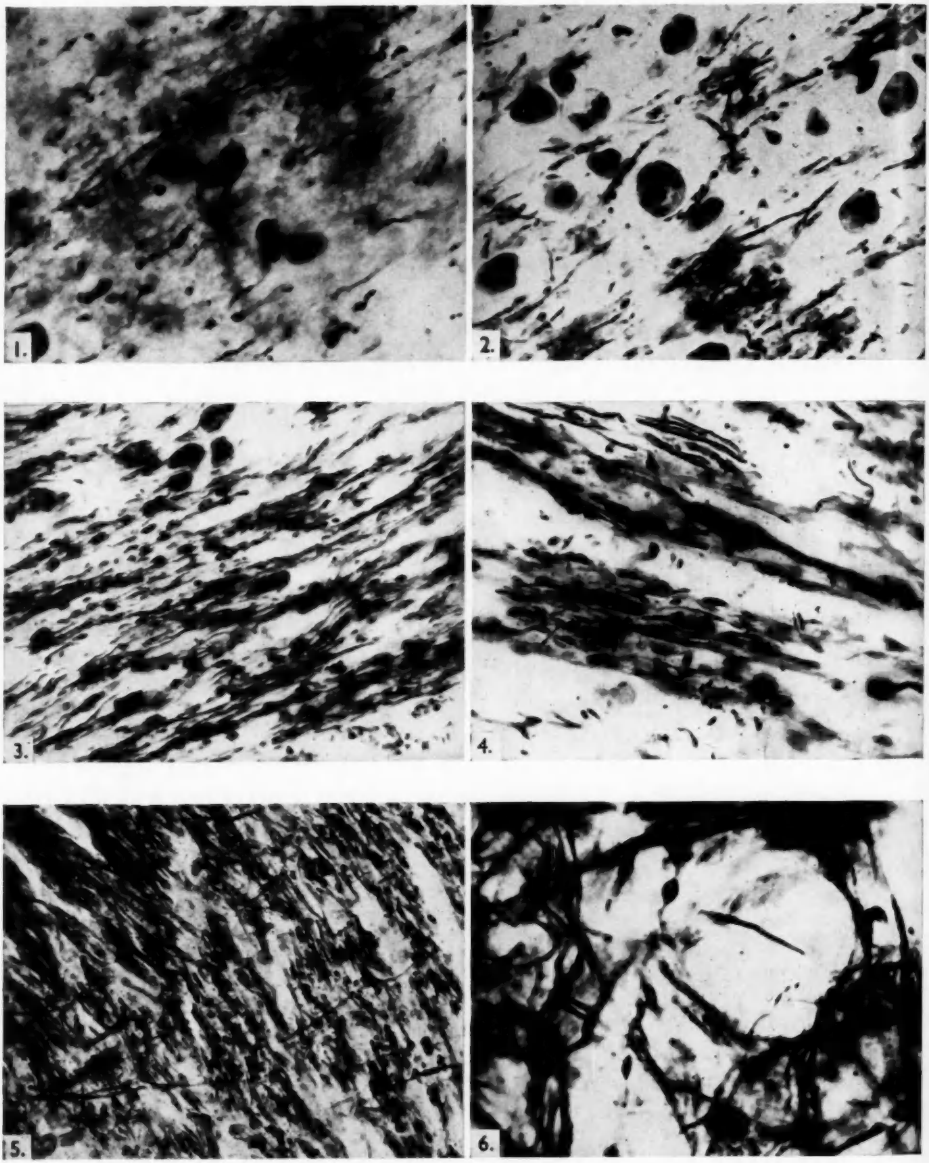
(5) Lesions in the anterior cingulate cortex produced severe degeneration in the cingulum extending posteriorly around the splenium of the corpus callosum to the upper part of the subiculum and presubiculum. Terminal degeneration was seen around the cells of the subiculum and presubiculum.

(6) Terminal degeneration in the posterior cingulate cortex was seen in laminæ I and IV following lesions in the anterior cingulate cortex.

Acknowledgments

I wish to extend my thanks to Professor W. E. Le Gros Clark for his helpful advice throughout and for the provision of all facilities for this

PLATE I



To illustrate article by W. R. Adey.

work. I also wish to thank Mrs. Margaret Meyer for her constructive criticism. Mr. L. Parke and Mr. R. Laing have given valuable assistance in staining the material used.

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PLATE I

FIG. 1.—Posterior cingulate ablation. Degenerating fibres in the first layer of the cortex of the presubiculum. (× 750.)

FIG. 2.—Posterior cingulate ablation. Degenerating terminals around the cells of layer II of the presubicular cortex. (× 530.)

FIG. 3.—Posterior cingulate ablation. Degenerating fibres in the dorsal part of the corpus callosum. These fibres run to the homologous area of the opposite hemisphere. (× 670.)

FIG. 4.—Anterior cingulate ablation. Degeneration in both medium and large-sized fibres of the cingulum in the region dorsal to the splenium of the corpus callosum. (× 670.)

FIG. 5.—Anterior cingulate ablation. Termination of the fibres of the cingulum in the superior part of the presubiculum. The normal fibres of the corpus callosum are seen superiorly on the left, sharply marked off from the degenerating cingulate fibres. (× 600.)

FIG. 6.—Anterior cingulate ablation. Drop-like degenerating terminals around the cells of the upper part of the subiculum. (× 1000.)

XUM

Notices of Recent Publications

Essay on the Cerebral Cortex. By G. von Bonin. Blackwell Scientific Publications Ltd. Oxford. 1950. Price 27s.

This brief monograph presents the general conclusions of the Professor of Anatomy of the University of Illinois upon the cerebral cortex considered structurally and functionally.

It reflects the growing revolt, to which the author has himself contributed, against the highly schematized cytoarchitectonics of the Vogts, and also reveals the growing spell of the "communication engineer" as one able to provide explanations of cortical processes.

Of the physiological insights of "The Integrative Action of the Nervous System" we find here no trace. How little influence has been exerted on some physiological thinking by Leyton and Sherrington's classic paper on the anthropoid cortex is shown with painful clarity in the author's statement that individual muscles are represented "only once" in fixed cortical points in area $FA\gamma$.

It is as disquieting as it is incredible that this should still be taught. So it is, however, and we may see in it physiological thought "advancing" backwards on its tracks to 1870, when excitable points in the cortex were first discovered and naïvely interpreted.

Twenty-seven shillings is a very great deal to have to pay for this suspension of the new in the obsolete.

The Physical Basis of Mind. A Series of Broadcast Talks compiled by Peter Laslett. Blackwell, Oxford. Price 5s.

It is unnecessary to say, perhaps, that these talks formed part of the Third Programme, and that a formidable array of talent was mustered to give them. The compiler admits that prior consultation between the speakers did not take place, and thus the co-ordinating function of science was presented to the listener in most unco-ordinate fashion and with much repetition. To find electrical impulses in almost every dish on the menu must have tasked the endurance of the audience.

The short introduction by Sir Charles Sherrington will be welcome to those older readers who recall with pleasure the quality of his thought, his modesty and his characteristic prose. He offers us no solution of the body-mind relationship in electronic terms, nor does he say with the two philosophers (Professors Ayer and Ryle) that there is no problem to solve.

Professor Adrian approaches the problem also with modest claims for the physiological method, but with complete clarity. Other scientific talks are by Professor Le Gros Clark, by Drs. Eliot Slater and Russell Brain and, finally, by Dr. Penfield who gives the listener some glimpses of his own special physiology of the diencephalon.

Lord Samuel attempts to hold the balance, where no balance is possible, between the views of the scientists, and those of the philosophers who say there is no body-mind problem but just some illogical ideas which have unnecessarily created one.

Perhaps the problem is one the scientists are not yet in a position to discuss with a lay audience since neither anatomy nor physiology provides the clue to its solution, while the philosophers, for their part, have too many and too easy solutions.

The listener with sufficient tenacity to stay the course, may well have found himself murmuring, as the last syllables fell from Professor Ryle who ended the series: "Myself when young did eagerly frequent Doctor and Saint, and heard great argument about it and about: but evermore came out by the same door as in I went," or, more tersely—with the Raven—"Nevermore."